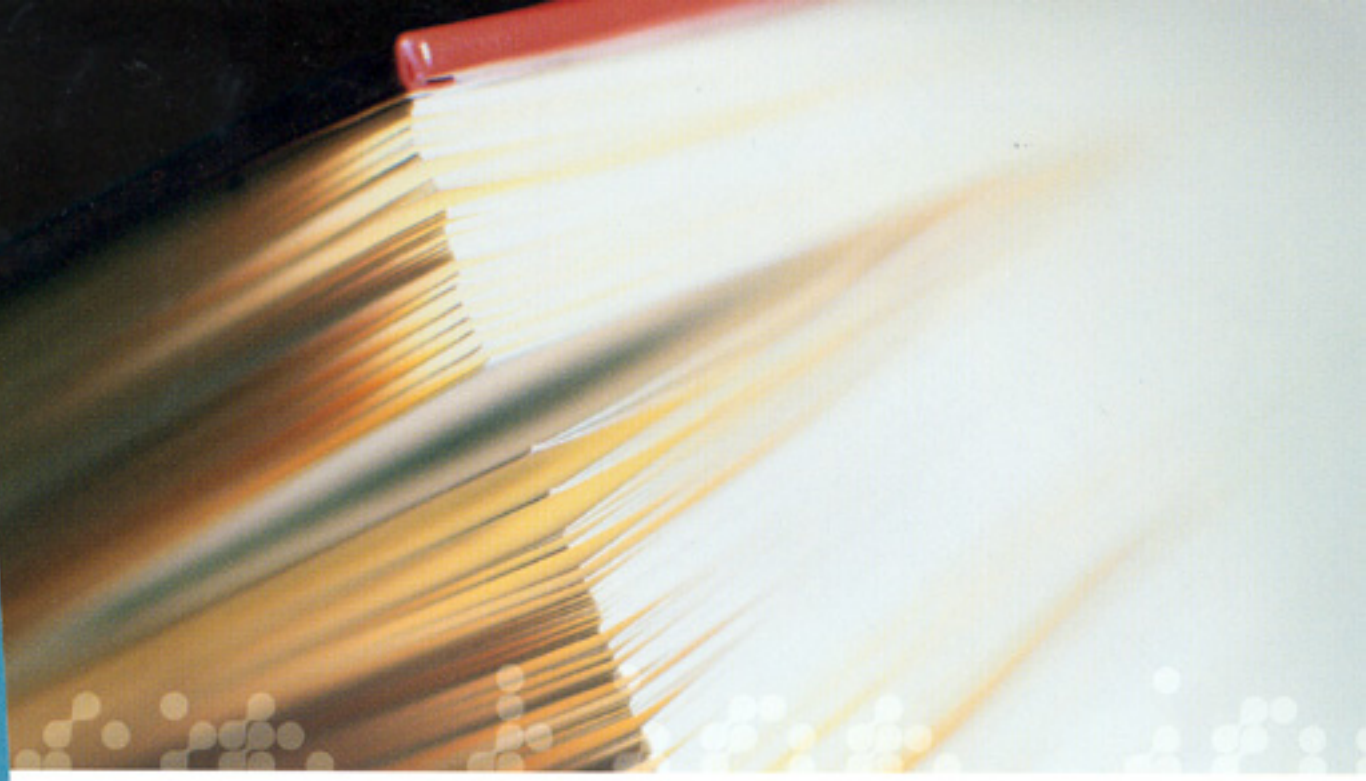

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INTERVAL CANCER IN WOMEN FOLLOWING A NORMAL INITIAL MAMMOGRAM IN THE QUEBEC BREAST CANCER SCREENING PROGRAM (PQDCS) IN 1998-2000

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SUMMARY

Interval cancers are cancers that are diagnosed during the interval between a negative screen and the subsequent screen. The rate of interval cancers is a performance indicator in the terms of reference of the Quebec Breast Cancer Screening Program (PQDCS). The PQDCS terms of reference do not set a standard for interval cancer rates, but the Evaluation Indicators Working Group, which monitors breast cancer screening programs in Canada, has determined that the rate of interval cancers should not exceed 6 cases of invasive cancer per 10,000 person-years within 12 months of a negative screen, or 12 cases per 10,000 person-years within 24 months of a negative screen.

The primary objective of this analysis was to estimate the rate of interval cancers among women who received an initial mammography in the PQDCS in 1998-2000 and whose mammogram was interpreted as normal (including non-equivocal benign lesions). The analysis also sought to identify the characteristics of women, radiologists and facilities that are associated with rising or decreasing early interval cancer rates (≤ 12 months post-screen), late interval cancer rates (13-24 months post-screen), and detection rates. Finally, the study was designed to compare the clinical and pathological characteristics of the three cancer groups: early interval cancers (diagnosed ≤ 12 months post-screen), late interval cancers (diagnosed 13-24 months post-screen), and screening-detected cancers.

The study looks at women who underwent screening mammography (referred to as the initial screening mammography) through the PQDCS between 1998 and 2000 and who signed a program consent form. Four groups of women were compared: screening-detected cancer; interval cancer diagnosed ≤ 12 months post-screen; interval cancer diagnosed 13-24 months post-screen; and controls. The “screening-detected cancer” group comprised all the women whose breast cancer (*in situ* or invasive) was detected at the time of their initial participation in the PQDCS between 1998 and 2000 (n=1,699). The “interval cancer” groups comprise all the women whose initial screening mammogram (1998-2000) was normal, but in whom breast cancer (*in situ* or invasive) was diagnosed in the post-screen period (n=165 ≤ 12 months post-screen; n=404, 13-24 months post-screen). The control group was selected from among the women whose initial screening mammogram was normal in 1998-2000 and who were not diagnosed with breast cancer during the post-screen period (n=48,200). Controls were randomly selected according to a ratio of 20 controls per case, with cases and controls matched on the basis of the quarter in which they were screened. Variables related to the characteristics of participants, radiologists and screening centres were derived from the PQDCS information system (SI-PQDCS). The data related to the clinical and pathological characteristics of cancer cases (both screening-detected and interval) were derived from pathology reports, the SI-PQDCS and the MedÉcho database. The data were analysed using logistic regression. In all of these analyses, odds ratio (OR) variances were corrected to account for intra-radiologist and intra-centre correlations in the interpretation of mammographic images.

Among PQDCS participants who had a normal initial mammogram between 1998 and 2000, the rate of invasive interval cancer was 6.4 and 11.6 per 10,000 woman-years respectively during the 12- and 24-month periods following a normal mammogram finding. In terms of proportional incidence, these rates correspond to 23.3% and 42.0% of the invasive breast cancer incidence observed in Quebec in 1997, before the PQDCS began.

The interval cancer rate tends to be higher among women with a higher risk of breast cancer, which means that rates of interval cancer increase with age and body mass index as well as with a family history of breast cancer or a history of breast biopsy.

Breast density is strongly associated with the interval cancer rate. This link is particularly strong in the year following mammography screening. In the 12-month period post-screen, the odds ratio for interval cancer is 13.00 (confidence interval (CI) at 95%: 6.79-24.89) in women with > 75% breast density, compared to those with less than 25% density. This observation confirms that breast density, while being a risk factor for breast cancer, may also mask certain cancers during screening, as well as limit the sensitivity of mammography.

Finally, the rate of interval cancer in the year following screening tends to decrease as a centre's screening volume increases. The interval cancer rate in the 12-month period post-screen is 37% lower in centres that perform 4,000 screens or more per year than in centres that perform fewer than 2,000 screens per year (OR: 0.63, CI 95%: 0.37-1.06); χ^2 trend: 3.70, p = 0.0546).

In conclusion, the frequency of interval cancers in the PQDCS (1998-2000) is comparable to that observed in other screening programs and meets the requirements of the Evaluation Indicators Working Group. Moreover, breast density greatly limits the capacity of screening mammography to detect cancer. This link between high breast density and reduced mammographic sensitivity has been observed in other studies and now represents the consensus view. Studies now underway in the United States and Europe should, in the coming years, help to identify measures to improve screening performance for women with very dense breasts. Finally, increased screening centre volume is linked to a higher detection rate and a lower interval cancer rate in the first year post-screen. These observations suggest that screening sensitivity increases with screening centre volume. It is important to understand the reasons behind this link, so that all centres can benefit from the advantages offered by centres with a higher screening volume.

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1. INTRODUCTION

The Quebec Breast Cancer Screening Program (PQDCS) will be successful in reducing the number of deaths attributable to breast cancer to the extent that screening—as practised in Quebec—provides an effective means of detecting a large proportion of the cancers present at the time of examination. This capacity to detect the presence of cancer is referred to as sensitivity. The greater the sensitivity, the greater the impact of the PQDCS on mortality. Sensitivity is not easy to measure directly, since it is impossible to know exactly how many cancers are actually present at the time of screening. The rate of detection is an indirect measure of sensitivity. A high detection rate indicates a high degree of sensitivity. Another indirect measure of screening sensitivity is the interval cancer rate. Interval cancers are cancers detected during the interval between a negative screen and the following screen. Unlike the detection rate, a low interval cancer rate is indicative of high sensitivity. Therefore, a low rate of interval cancer in the PQDCS would indicate, on the one hand, that the screening being carried out in the PQDCS is highly sensitive and, on the other hand, that the Program's chances of reducing breast cancer mortality are that much greater.

The rate of interval cancers is one of the performance indicators in the Program's terms of reference (1). The PQDCS terms of reference do not set a standard for interval cancer rates, but the Evaluation Indicators Working Group, which monitors breast cancer screening programs in Canada, has determined that the interval cancer rate should not exceed 6 cases of invasive cancer per 10,000 person-years within 12 months of a negative screen, or 12 cases per 10,000 person-years within 24 months of a negative screen (2).

The primary objective of this analysis was to estimate the interval cancer rate among women who had an initial mammography as part of the PQDCS in 1998-2000 and whose mammogram was interpreted as normal (including non-equivocal benign lesions). The analysis also sought to identify the factors associated with high or low interval cancer rates. The factors considered included characteristics of participants, radiologists and designated screening centres (DSCs).

This analysis deals only with the frequency of interval cancer diagnosed following a normal screening mammogram. The literature on interval cancer normally looks at interval cancer following a negative screen. A normal screening mammogram and a negative screening mammogram are not the same thing. Negative screens include situations in which a screening mammogram has been interpreted as normal (including non-equivocal benign lesions), but they also include situations in which a screening mammogram is first interpreted as abnormal and is followed by an investigation in which the radiological anomaly is determined to be negative, which is to say that no cancer is uncovered. We have not included in this study cases of interval cancer that are diagnosed subsequent to an abnormal mammogram, since the analysis of interval cancer in these cases is very complex. Indeed, an abnormal screening mammogram is soon followed by an investigation. In the course of this investigation, approximately 5-6% of women will receive a diagnosis of breast cancer (screening-detected breast cancer) (1). Among the women whose investigation results are negative, PQDCS data show that 30% are kept under observation for several months and

that cancers detected as a result of such monitoring may be classified as screening-detected cancers or as interval cancers (3). The information currently available on the monitoring of women with negative investigation results is not comprehensive. Consequently, it is difficult, with the information presently available, to determine whether cancers diagnosed as part of this monitoring should be classified as screening-detected cancers, or as interval cancers.

Although we have only studied interval cancers diagnosed in women with a normal mammogram, the rates observed in this group are very similar to those observed in all women with a negative screen since women with a normal mammogram represent approximately 90% of all women with a negative screen (3). The rate of interval cancer following a normal mammogram finding can therefore be compared to the standards set for this rate.

Interval cancers constitute a heterogeneous group of cancers. Several classifications of interval cancer have been proposed (4-13). These classifications can be summarized as follows:

- The first group comprises interval cancers that were not visible on screening mammography. Some of these interval cancers simply were not present at the time of screening. Other interval cancers in this group, particularly those detected in the year following a negative screen, were already present but did not show perceptible signs on the mammogram due to the limitations inherent to this type of examination. Mammography is the best breast cancer screening method available at present, but it does not detect all cancers. Finally, other interval cancers in this first group do not show up on a mammogram due to sub-optimal mammographic technique, such as poor positioning.
- A second group includes interval cancers that were present at the time of screening and showed signs on the screening mammogram, albeit signs that were minimal and non-specific. Even radiologists who are experts in screening mammography would not have classified these lesions as suspicious.
- Finally, the third group comprises interval cancers that were present at the time of screening and presented signs on the screening mammogram that would have been deemed suspicious by radiologists with expertise in screening mammography, but somehow went undetected. It may be that the radiologist who read the mammogram did not recognize the signs or, conversely, that the radiologist did recognize the signs but the cancer was not diagnosed in the subsequent investigation.

In this project, no attempt was made to classify interval cancers according to the above categories. The classification of interval cancers requires the use of a highly rigorous protocol to review screening mammograms and mammograms done subsequent to the diagnosis of interval cancer. No review of screening or diagnostic mammograms was carried out as part of this project.

2. CURRENT KNOWLEDGE ON INTERVAL CANCERS

2.1. Frequency of interval cancers following a negative screen

Taylor and colleagues (14) have summarized the studies that deal with the frequency of interval cancers in the 12-month period following mammography, with or without an additional clinical breast examination. These studies include randomized screening mammography trials carried out in Scandinavia, Scotland, Canada (National Breast Screening Study (NBSS) 2 – women aged 50 to 59 years) and the United States, as well as data from a variety of screening programs in countries such as the Netherlands, Australia, Italy, Denmark and the United Kingdom.

The frequency of interval cancers is often expressed in terms of proportional incidence. This measure takes into account the fact that incidence of breast cancer can vary from one population to the next. Proportional incidence corresponds to the ratio between the incidence of interval cancer observed among women who have had a negative screen and the projected incidence of breast cancer in the same population in the absence of screening. For example, a proportional incidence of 25% indicates that the incidence of interval breast cancer is equal to 25% of the breast cancer incidence that would have been observed in the same population if screening were not available. In the year following a negative screen, the proportional incidence of interval cancer ranges from 7% (Ostergotland) to 31% (NBSS 2) in experimental studies, and from 13% (Florence) to 45% (Nijmegen) in non-experimental studies. A meta-analysis of experimental studies (6 studies) produced a proportional incidence estimate of 19% (13% when limited to Swedish experimental studies). The meta-analysis of non-experimental studies (13 studies) produced a proportional incidence estimate of 27% with more than half of these studies producing an estimate above 25%. The differences between the estimates derived from these two types of studies result from the variable comprehensiveness of cancer case reporting, as well as from the procedure used to estimate the projected incidence of breast cancer in the absence of screening. Projected incidence is derived from the control group in experimental studies, but is usually derived from modelling in non-experimental studies.

2.2. Typology of the studies and primary observations

The studies on interval cancer generally seek to achieve four primary objectives: (1) one category includes studies that document the frequency of interval cancers in various screening programs; (2) a second category of studies seeks to classify interval cancers according to their relative detectability on the preceding screening mammogram, usually according to the location of the tumor or the technical quality of the mammogram image; (3) a third group of studies is designed to estimate the clinical or pathological characteristics (size, stage, proliferation markers, etc.) of interval cancers, compared to cancers detected by screening or those diagnosed in unscreened populations. This objective is frequently combined with that of the final group of studies, which includes (4) survival analyses.

A number of observations can be made with respect to these studies. For one thing, the frequency of interval cancer tends to increase in proportion to the time elapsed since the last screening (15-17). For example, Wang and colleagues (16) report a rate of 4.6 per 10,000 women screened in the 12-month period following a negative screen, and 13.6 per 10,000 during the subsequent 12-month period.

The frequency of interval cancers varies depending on whether one is looking at initial screens or subsequent screens, as well as on the number of screening cycles (18). This relationship is fairly complex and depends on the combined, albeit opposite, influence of two factors. On the one hand, the availability of prior mammographic images improves cancer detection (19), which should minimize the proportion of interval cancers present at the time of screening. On the other hand, the frequency of breast cancer—some cases of which will manifest between two screening episodes as interval cancers—increases with age (20), which in turn correlates with the number of screening cycles in the program. Thus, in the Canadian study (NBSS 2) of women between the ages of 50 and 59 (21), the rate of interval cancers in the experimental group exposed to mammography declined from 7.6 to 5.7 and 4.6 per 10,000 woman-years, following the first, second and third mammographies, subsequently stabilizing at 5.2 and 5.1 per 10,000 after the fourth and fifth screens. In the NBSS 1 study, which included women aged 40 to 49 years (22), these figures were, respectively, 7.5, 7.1, 3.6, 4.6 and 6.4 per 10,000 woman-years. The same downward trend in interval cancer rates was observed between the first and second screening in various European programs currently underway (23).

Interval cancers often tend to be small tumors that are difficult to visualize due to their location; they tend to be visible in only one view and appear benign, without desmoplastic reaction (as is frequently the case with lobular tumors), and tend to be stable, with or without slow growth on successive images (24,25). The frequency of breast cancers that show retrospective signs on earlier mammograms varies in these studies from 22% to 75% (26). This proportion tends to vary according to the method used to review screening mammograms (consensus, majority, or other) and to determine whether there were radiological signs on the screening mammogram and whether these signs were suspicious or not (7,12). The proportion of interval cancers that show minimal/non-specific or suspicious signs on screening mammograms is also variable (6,12,27,28). According to Saarenmaa (26), 19% of interval cancers were visible at the time of the previous screen. Moreover, tumors that manifest soon after a negative screen are more likely to correspond to cancers that were present at the time of screening but were not detected (4,27).

As expected, the factors that influence mammographic sensitivity are associated with the interval cancer rate. As mentioned earlier, sensitivity relates to the capacity of mammography to detect breast cancer when present. When mammographic sensitivity is high, the frequency of interval cancers tends to be low. For example, mammographic sensitivity is lower in women who have dense breasts and in those who are receiving hormone replacement therapy. Therefore, it is not surprising to learn that the frequency of interval cancers is higher among these women (4,10,11,13,16,29-31).

Moreover, the proportion of tumors with microcalcifications and the proportion of *in situ* tumors or tumors with a significant *in situ* component are smaller in the case of interval cancers than in cancers detected by screening mammography (8,10,11,16,26,31,32). Cancers that progress rapidly have a greater chance of being diagnosed in the interval between two screens. Studies that examine tumor characteristics—be they clinical, pathological (size, stage), or biological (proliferation indices, grade)—show that interval cancers are frequently aggressive, compared with cancers detected through screening or after symptoms have appeared (3,8,9,11,16,29,31-35).

In the Malmö study (36), the prognosis for interval cancers was poorer than for other cases of breast cancer among participants, namely cases detected by screening mammography in the experimental group and cases diagnosed after the appearance of symptoms in the control group. In fact, the risk of mortality for women with interval cancer was 2.3 times higher after adjustment for age and stage of illness, than that of cases diagnosed among the control population. In four other studies, however, interval cancer survival rates were comparable to those of clinical cases diagnosed in an unscreened population (33,35,37,38). Brekelmans and colleagues (35) performed an analysis by interval cancer sub-group and found significantly different survival rates between interval cancers that did not present signs on the screening mammogram and those detected by mammography. These cases of interval cancer also showed a poorer survival rate than those which already presented suspicious signs on the mammogram; however, this difference was not statistically significant (ten-year survival rates of 58% and 67% respectively, p=0.38).

2.3. Summary of current knowledge

A number of factors influence interval cancer rates and these factors need to be taken into account in interpreting the present study and in comparing its results with those found in the larger literature on interval cancers.

1. The time interval between screening examinations varies according to location. It is therefore best to express the frequency of interval cancers in terms of specific post-screen periods (e.g.: ≤ 12 months post-screen, 13-24 months post-screen, etc.).
2. The definition of interval cancer varies from study to study. In particular, inclusion of the Bi-Rads 3 category (probably benign mammogram and recommendation of short- or medium-term follow-up) is not consistent. In some studies (14,32), a women diagnosed after her mammogram is categorized as Bi-Rads 3 is included among interval cases, while in others (30,31), these cancers are viewed as having been detected through screening and therefore are not counted as interval cancers.
3. The frequency of interval cancers differs for initial and subsequent screens and according to the number of screening cycles (18), but outcomes and performance standards are frequently provided in a global fashion, without accounting for this variable.
4. The thoroughness of cancer case reporting and the quality of local tumor registries varies from place to place. The greater the thoroughness of the tumor registry, the greater the frequency of interval cancers is likely to be.

5. The procedure used in the studies to project the incidence of breast cancer in the absence of screening tends to vary (incidence in a similar population, incidence estimates derived from projections, etc.). Consequently, proportional incidence may vary according to the method selected to project breast cancer incidence in the absence of screening.
6. The inclusion of a clinical breast examination along with screening mammography influences the detection of cases and the frequency of interval cancers.
7. The frequency of interval cancers tends to increase in populations where the incidence of breast cancer is high.
8. The frequency of interval cancers within a given population varies according to the characteristics of the women that compose the population. Women at higher risk of breast cancer will also have a higher rate of interval cancer. Similarly, women with characteristics that limit mammographic sensitivity tend to have a higher rate of interval cancer.
9. Certain technical parameters of screening mammography, such as the number of images produced, as well as certain para-technical parameters, such as double reading or the decision-making process of readers (consensus, unanimity, majority, or individual) can influence test sensitivity, as well as interval cancer rates.
10. Finally, the inclusion of *in situ* tumors with interval cancers is not consistent in the studies.

3. OBJECTIVES

The primary objective of this study was to characterize the phenomenon of interval cancer in women whose initial mammography through the Quebec Breast Cancer Screening Program (PQDCS) (1998-2000) was deemed to be normal.

The specific objectives of this study were as follows:

1. Estimate the frequency of interval cancers in women whose initial mammography was normal.
2. Identify the characteristics of participants, radiologists, and centres that influence the rate of interval cancer ≤ 12 months post-screen, the rate of interval cancer 13-24 months post-screen, and the detection rate (the detection rate is also examined because—like the interval cancer rate—it is an indirect measure of sensitivity).
3. Evaluate the consistency of these associations from one type of cancer to another (≤ 12 months post-screen, 13-24 months post-screen, or detected by mammography).
4. Compare the biological and pathological characteristics of three groups of cancers: early interval cancers (diagnosed ≤ 12 months post-screen), late interval cancers (diagnosed 13-24 months post-screen), and screening-detected cancers.

4. MATERIALS AND METHODS

This study looks at women who received an initial screening mammography under the Quebec Breast Cancer Screening Program (PQDCS) in 1998-2000 and who signed a program consent form. Only information from this initial mammography is used to define the study groups. Some women underwent a second mammographic examination (referred to as a subsequent screening mammography) during this period, but the data concerning these later examinations are not included in this study. The procedure for identifying cancer cases detected by mammography has been validated and described (39). A similar approach is used here for the identification and clinical characterization of interval cancers (Appendix 1).

Only women who are asymptomatic, who have no breast prosthesis and no history of mastectomy, and whose screening mammograms were interpreted by a radiologist identified in the program's information system (SI-PQDCS) were selected for this study; their respective breast cancer risk levels were not taken into account. Four groups of women were compared: screening-detected cancer; interval cancer diagnosed ≤ 12 months post-screen; interval cancer diagnosed 13-24 months post-screen; and controls. The "screening-detected cancer" group comprised all the women in whom breast cancer (*in situ* or invasive) was detected by screening at the time of their initial participation in the PQDCS between 1998 and 2000 (n=1,699). The "interval cancer" groups comprise all the women whose initial screening mammography (1998-2000) was normal, but in whom breast cancer (*in situ* or invasive) was diagnosed in the post-screen period (n=165, ≤ 12 months post-screen; n=404, 13-24 months post-screen). The post-screen period considered for interval cancers began on the date of the normal screen and ended when the first of the following events took place: a diagnosis of breast cancer, a subsequent screening mammography episode, the second anniversary of the initial screening mammography (24 months post-screen), or December 31, 2001. Finally, the control group was selected from among the women whose initial screening mammography was normal in 1998-2000 and who were not diagnosed with breast cancer during the post-screen period (n=48,200). Controls were randomly selected according to a ratio of 20 controls per case, with cases and controls matched on the basis of the quarter in which they were screened.

The data concerning the clinical and pathological characteristics of cancers (screening-detected and interval) were derived from different sources, according to cancer type, as described in Appendix 2. These data include: tumor laterality, tissue sample dates and types, tumor invasiveness and size, histological type, histological grade, vascular invasion, architectural aspect, nuclear grade, maximum diameter, presence of necrosis or microinvasion in the case of *in situ* tumors, and details regarding lymph node dissection. Moreover, the presence and location of mammographic anomalies, as well as the view(s) and number of images on which these were visible were also noted.

The variables relating to the characteristics of participants, radiologists and screening centres included: (for participants): age, parity, menopausal status, family history of breast cancer, body mass index, use of hormone replacement, breast density, earlier breast interventions (puncture/biopsy or breast reduction), mammography/clinical breast

examination history; (for radiologists): sex and year of certification in radiology, the type of screening centre in which they practise (radiology clinic or hospital), their personal volume of mammogram reading, the number of clinics in which they practised during the period, their referral and detection rates and those of colleagues at the primary practice site; (for centres): the annual screening volume of the centre where the examination took place. These variables are part of or can be estimated on the basis of the SI-PQDCS; they have been used in earlier evaluative studies of the PQDCS.

The data were analysed using logistic regression, with the examination quarter included in all models and adjustments made for potentially confounding variables. Since the radiologist's detection rate is an indirect measure of sensitivity, this rate can be viewed as an intermediate variable in the association between certain characteristics of the radiologist or screening centre (for example the volume of screening mammography) and the rate of interval cancers. Consequently, the detection rate of radiologists is not included in the models designed to evaluate these associations. Our analysis was also limited to invasive tumors (Appendix 3, tables 7 and 8), but this has not appreciably altered the results. The measure of association is the odds ratio (OR). In comparing screening-detected cancers with the control population, the OR can be interpreted as an approximation of the detection rate ratio, even though the control group is entirely composed of cancer-free women with normal mammograms, whereas the detection rate is calculated using a population that includes all screening participants. This approximation is justified by the fact that cancer-free women with normal mammograms represent approximately 90% of screening participants. Nonetheless, the nature of the control group may explain certain (largely minimal) differences in the strength of the associations presented in this report and in earlier publications of the evaluation team. In comparing interval cancer and control group data, the OR can be interpreted as an approximation of the incidence rate ratio (incidence density) of interval cancer. In all the analyses, OR variance has been corrected to account for intra-radiologist and intra-centre correlations in the interpretation of mammographic images. The data were analysed with the aid of SAS version 8.2 software, using a bilateral statistical significance threshold of 5%.

5. RESULTS

5.1. Frequency of interval cancers following a normal initial mammogram

Table 1 summarizes the frequency of interval cancers observed in the Quebec Breast Cancer Screening Program (PQDCS) among women who received a normal initial mammogram between 1998 and 2000. The incidence rate of invasive and *in situ* tumors combined for the entire period of ≤ 24 months post-screen, expressed as the number of new cases per 10,000 woman-years of observation, is 12.8 (confidence interval (CI) 95%: 11.8-13.8). The interval cancer rate increases according to the time elapsed post-screen, rising from 7.1 (CI 95%: 6.1-8.1) during the first 12 months, to 19.9 (CI 95%: 18.1-21.7) between months 13 and 24, and reaching 33.4 per 10,000 during the period of 25-36 months post-screen among the women who did not have a subsequent screen in accordance with program recommendations.

The incidence of invasive interval tumors is 6.4 and 11.6 per 10,000 woman-years in the ≤ 12 and ≤ 24 month post-screen periods, respectively. In terms of proportional incidence, these rates represent 23.3% (CI 95%: 20.2%-27.0%) and 42.0% (CI 95%: 38.8%-45.5%) of the incidence of invasive breast cancer observed in 1997, prior to the launch of the PQDCS (Source: *Fichier des tumeurs du Québec*).

Generally speaking, the incidence of interval cancer tends to increase with age, which reflects the increased incidence of breast cancer in older women (Table 1). Among women diagnosed within 12 months of mammography, however, incidence is lower for older women (65-69 years), which is probably attributable to the greater sensitivity of mammography in this group (40).

5.2. Clinical and pathological characteristics of interval cancers diagnosed following a normal mammogram/screening-detected cancers

Table 2 summarizes the primary characteristics of cancers detected through the program and interval cancers discovered following a normal mammogram. These data are based on the pathology reports of 1,507 (88.7%) of the 1,699 cases screened, and 556 (97.7%) of the 569 cases of interval cancer observed. Not all the cancers are included in this analysis, because some pathology reports did not contain all the required information. The percentage of cancers with missing data is therefore fairly large for a few variables, which imposes limitations on the interpretation of these data.

Several differences are evident among the three cancer groups. The proportion of invasive tumors is clearly larger for interval cancers than for screening-detected cancers (92.6% vs. 79.0%; $p < 0.0001$). Invasive interval cancers are also larger at the time of diagnosis (average size = 2.05 cm) than those detected through screening (1.39 cm; $p < 0.0001$). The proportion of small tumors (1 cm or less) is 21.5% for interval cancers and 43.7% for screening-detected cancer ($p < 0.0001$). Moreover, among the cancers for which tumor

extension to the axillary ganglia was evaluated, 42.6% of interval cancers and 25.2% of screening-detected cancers showed tumoral invasion of the axillary ganglia ($p < 0.0001$). Finally, the proportion of large tumors or tumors with regional extension tends to be greater for interval cancers diagnosed ≤ 12 months post-screen than those diagnosed 13-24 months post-screen. Interval cancers also present histological characteristics that suggest more aggressive behaviour, including a larger percentage of histological grade 3 tumors (34.2% vs. 14.4% of screening-detected cancers; $p < 0.0001$) and tumors with vascular invasion (40.9% vs. 20.7%; $p < 0.0001$). The overrepresentation of lobular tumors in interval cancers (13.8% of interval cancers vs. 8.8% of screening-detected cancers; $p= 0.0046$) is compatible with the low detection potential for such tumors using mammography. Moreover, as one would expect, the proportion of lobular tumors with a favourable prognosis is almost three times larger in screening-detected cancers than in interval cancers (7.2% vs. 2.6%) ($p= 0.0009$) (41).

5.3. Characteristics of women with breast cancer and control group women

Table 3 presents the numbers and characteristics of women with breast cancer (screening-detected and interval) and women in the control group. Table 4 presents the results of the multivariate analyses. Unless otherwise indicated, ORs are derived from a mathematical model that includes all of the women's characteristics, as presented in this table, as well as the characteristics of radiologists and screening centres, as presented in tables 5 and 6. As indicated earlier, ORs derived from the comparison of women with screening-detected breast cancer and women in the control group (see odds ratios in the column entitled "Screening-detected cancers) are estimates of the detection rate ratio. For example, women aged 65-69 have a OR of 1.76. This OR signifies that the detection rate among women aged 65-69 is approximately 1.76 times higher than that observed in women aged 50-54 (the comparison group, with a OR of 1.00). Thus, the detection rate for women aged 65-69 has increased by 76% compared to women in the 50-54 age group. This odds ratio of 1.76 is statistically significant since its confidence interval (95%) does not include the 1.00 value. Moreover, the ORs derived from the comparison of women with interval cancers and women in the control group relate to interval cancer rates in the first and second year post-screen. For example, the interval cancer rates for women aged 65-69 in the year following a normal screen (≤ 12 months post-screen) are 1.75 times higher than those of women aged 50-54. In the second year post-screen (13-24 months), the rate of interval cancer is 1.64 times higher for women aged 65-69 than for those aged 50-54.

For several characteristics, both detection and interval cancer rates tend to be higher in women with a higher incidence (risk) of breast cancer. We know, for example, that the incidence of breast cancer increases with age (20). Therefore, it is not surprising to find that detection and interval cancer rates also increase with age (Table 4). Similarly, the detection rate in women who carried their first pregnancy to term before age 25 is lower (OR: 0.64) than that of nulliparous women, whereas the detection rate in women with late pregnancies is comparable to that of nulliparous women. This trend is also observed for the interval cancer rate in the 13-24-month period following a normal screen and is comparable to that observed with regard to breast cancer risk (20). We also observe that increased body mass index is

associated with an increased detection rate and an increased interval cancer rate. Thus, we find that, compared to women with a low body mass index (< 20.0 kg/m^2), those with a high body mass index (≥ 35 kg/m^2) show higher detection and interval cancer rates, whether in the first or the second year after screening (ORs: 2.19, 2.20 and 1.85 respectively). Similarly, detection and interval cancer rates are higher among women who have previously undergone a breast biopsy than among those who have never had a biopsy. The increase with respect to detection rate is 41%; for interval cancer, the increase is 64% in the first year and 52% in the second year following a normal screen. Among women aged 50-69, increased body mass index and a history of breast biopsy are associated with a higher risk of developing breast cancer (20).

However, associations between certain other characteristics and the rate of detection and the rate of interval cancers ≤ 12 months and/or 13-24 months post-screen cannot be explained solely by differences in incidence level or breast cancer risk. For example, the detection rate in women who have never undergone mammography is 1.81 times higher than the rate for women with a history of mammography. However, the interval cancer rate for both the first and second year post-screen was found to be the same, regardless of whether or not the subjects had undergone mammography in the past (ORs: 0.95, 0.94, respectively). Although study participants underwent an initial mammography through the PQDCS, 82% had undergone mammography in the past. The rate of detection is usually higher for a first screening mammography than for a subsequent mammography when the interval between the two examinations is less than approximately three years (2.42). According to the PQDCS terms of reference, for example, the projected detection rate for an initial screening mammography is 5.0 per 1,000, while for subsequent mammographies it is 3.5 per 1,000 (2). It is therefore likely that this phenomenon explains the association observed between a history of prior mammography and the rate of detection.

The recommended frequency of screening mammography (annual vs. biennial) can also influence results. Two examples of this phenomenon are possibly a family history of breast cancer and the use of hormone replacement therapy. The rate of interval cancer 13-24 months following a normal screen is greatly increased (OR: 2.45), while the rate of interval cancer ≤ 12 months post-screen is only slightly increased (RC: 1.26) in women who have a family history of breast cancer. Similar differences can be observed in the case of hormone replacement therapy. Women who indicate that they are receiving hormone replacement therapy at the time of screening have a slightly higher risk of developing interval cancer in the period ≤ 12 months post-screen, but this increase is larger in the period of 13-24 months following a normal screen (ORs: 1.18 and 1.49 for interval cancer ≤ 12 and 13-24 months post-screen respectively). This likely can be explained—at least in part—by variations in the recommended frequency of screening mammography (annual vs. biennial). It is indeed quite plausible that doctors tend to prescribe annual mammography when certain risk factors for breast cancer are present. In 1998-2000, the PQDCS did not allow for annual screening mammography. Some of these mammographies were being erroneously identified as diagnostic mammographies and, in our analyses, the cancers detected through these examinations were being identified as interval cancers rather than screening-detected cancers. It is impossible to quantify the scale of this phenomenon and thereby determine the extent to which the risk of interval cancer in the 13-24 month post-screen period was

overestimated. However, this phenomenon should not affect the increase in the interval cancer risk in the period 12 months post-screen. The latter is probably linked to family history and hormone replacement therapy, which are know risk factors for breast cancer (20,43).

Finally, any factor that reduces mammographic sensitivity should result in a higher interval cancer rate. Breast density is associated with a substantially higher rate of interval cancer ≤ 12 months post-screen. The OR for early interval cancer (≤ 12 months post-screen) is 13.00 (CI 95%: 6.79-24.89) in women with > 75% breast density, compared with that of women with less than 25% density. For interval cancers diagnosed 13-24 months post-screen and cancers detected by mammography, the increase in the OR is much less (ORs: 3.29 (CI 95%: 2.26-4.79) and 1.77 (CI 95%: 1.41-2.22) respectively), although it is still statistically significant. It may be that the strong association between breast density and the rate of interval cancer ≤ 12 months post-screen is primarily due to the fact that breast density masks certain cancers and limits the ability of mammography to detect these cancers, while also being a risk factor for breast cancer (44-47).

5.4. Characteristics of radiologists and screening centres

Table 5 summarizes the distribution of cancer cases and controls based on the characteristics of the radiologists who interpreted the mammograms and the screening centres where the procedures took place. Women with cancer and controls appear to differ in terms of certain variables, but the differences are difficult to interpret, either because they are relatively weak, or because the number of interval cancer cases is small. What is more, the differences observed have been adjusted for the women's characteristics.

Table 6 presents the results of the multivariate analyses. Due to the adjustment for the women's characteristics and the other variables related to the radiologists and screening centres which are incorporated into this table, the associations observed cannot be explained by these factors. However, a bias attributable to variations in the practice of annual mammography may influence certain associations observed with respect to the interval cancer rate 13-24 months post-screen. Once again, this bias cannot be quantified, but it has likely resulted in an overestimation of some ORs.

The easiest results to interpret are therefore those that relate to the detection rate and interval cancer rate ≤ 12 months post-screen. In theory, when screening sensitivity is high, the detection rate should necessarily be high as well, while the rate of interval cancers ≤ 12 months post-screen should be low. When a variable is associated with an increased rate of detection and reduced rate of interval cancers ≤ 12 months post-screen, it is far more clear that the variable in question is truly linked to greater screening sensitivity.

As expected, the interval cancer rate ≤ 12 months post-screen declines when a radiologist's average detection rate is high. The detection rate is 3 times higher (OR: 3.54 (CI 95%: 3.14-3.98), χ^2 trend: 503.11, $p < 0.0001$) when a mammogram is interpreted by a radiologist whose average detection rate is greater than 8.0/1,000 than by a radiologist with an average detection rate under 4.0/1,000. Similarly, the interval cancer rate ≤ 12 months post-screen

also tends to decrease as a radiologist's average detection rate increases, although this relationship is not quite statistically significant in the present study (χ^2 trend: 2.63, p = 0.1046).

Among the other characteristics featured in Table 6, only screening centre volume was consistently associated with the rate of detection and the rate of interval cancer ≤ 12 months post-screen. Larger volume of screening in the centre is associated with a higher cancer detection rate. In fact, the detection rate is 41% higher in centres that perform 4,000 screening examinations or more per year than in centres that perform fewer than 2,000 screening examinations per year (OR: 1.41; χ^2 trend: 14.08, p = 0.0002). As expected, when the association observed with the detection rate is attributable to improved sensitivity, an increase in centre volume should be associated with a reduced rate of interval cancer ≤ 12 months post-screen. The interval cancer rate ≤ 12 months post-screen is 37% lower in centres that perform 4,000 or more screening examinations yearly than in centres that perform fewer than 2,000 examinations yearly (OR: 0.63; χ^2 trend: 3.70, p = 0.0546).

Radiologists who read larger numbers of screening mammograms (1,500 mammograms or more per year) have a 13-24 month interval cancer rate that is lower than that of radiologists who read fewer screening mammograms each year (OR: 0.60 for those who read at least 1,500 mammograms each year versus those who read fewer than 500), and the trend in this volume-associated reduction is almost significant from a statistical standpoint (p= 0.0801). This observation is difficult to explain since the reading volume of radiologists is not associated with the detection rate nor with the interval cancer rate ≤ 12 months post-screen, which suggests that this factor is not independently associated with screening sensitivity.

6. DISCUSSION

This analysis reveals that the incidence of interval cancer among women who had a normal initial mammogram between 1998 and 2000 is close to the Canadian norm, which is 6.0 and 12.0 cases of invasive cancer per 10,000 woman-years of observation within 12 and 24 months of a negative screen (with a normal or abnormal mammogram). The incidence of invasive tumors in the present analysis is 6.4 and 11.6 per 10,000 within 12 and 24 months of screening. These numbers suggest that the frequency of interval cancer in Quebec is consistent with Canadian standards. However, the estimates provided here only take into account the interval cancer rate for women whose screening mammogram was interpreted as normal. The comparison of interval cancer rates in Quebec with Canadian standards will need to be reviewed following the inclusion of women with abnormal mammographies whose subsequent investigation results were negative. Moreover, the incidence observed 25-36 months post-screen (33.4 per 10,000) is comparable to that observed in Quebec women between the ages of 52 and 72 before the Quebec Breast Cancer Screening Program (PQDCS) began in 1997 (29.9 per 10,000). This clearly demonstrates how important it is for women to comply with recommendations concerning screening frequency, namely the two-year recall.

As expected, the pathological and biological characteristics of interval cancers, as indexed in this study, suggest that these cancers tend to be more advanced at the time of diagnosis, and are frequently more aggressive than cancers detected through screening. Since women's first screening episode is associated with the detection of prevalent cancers, which also tend to be more indolent in terms of their clinical course, one may assume that the differences between screening-detected cancers and interval cancers will be less marked when analysis is repeated for subsequent screening cycles. On the whole, the parameters of cancers detected by screening are consistent with the standards established in the terms of reference of the PQDCS (1).

The importance of several cancer risk factors is obvious in this study, for both screening-detected cancers and interval cancers diagnosed following a normal mammogram. This explains the association of both screening-detected cancer and interval cancer with factors such as age, reproductive variables, body mass index in a largely menopausal population, and a history of breast biopsy.

The frequency of interval cancers 13-24 months post-screen is probably overestimated due to the incorrect classification of certain yearly screening mammograms as diagnostic mammograms, resulting in the inclusion of cancers detected by screening mammography as interval cancers. This error, although difficult to quantify, results in a bias which in turn leads to the exaggeration of certain associations between interval cancer occurring 13-24 months post-screen and factors that are sometimes interpreted as indications that surveillance needs to be stepped up (most notably through annual mammography) for women at higher risk of developing breast cancer. Two such factors are a family history of breast cancer and the use of hormone replacement therapy.

The frequency of interval cancer ≤ 12 months post-screen is influenced by the masking effect of high breast density, as shown by the sharp rise in ORs as breast density increases. Diminished mammography performance with increased breast density is a documented limitation of this screening examination (30,48-53). It has been estimated that mammographic sensitivity declines from 98% in women with fatty breasts to merely 48% in women whose breasts are extremely dense (48). Adjustment for age and hormone replacement therapy does not eliminate this gradient (48,49). Recently published clinical studies (54) and other studies that are currently underway (55) should document the usefulness of alternative or complementary forms of testing (e.g., breast ultrasound) for women with dense breasts. Recommendations concerning the use of these tests should be based on the entire range of evidence that will become available within the next few years, as well as the feasibility and efficiency of resorting to these options on a populational basis. In the interim, women need to be informed about the inherent limitations of screening mammography and encouraged to undergo an annual clinical breast examination, as recommended by several organizations that combat cancer and work to improve clinical practices (56,57).

The relationship between breast cancer detection with mammography and the performance indicators of radiologists was to be expected. Consequently, it is logical to observe that the risk of interval cancer decreases as a radiologist's individual detection rate increases, particularly in the period immediately following the mammography. However, no point estimate of association was significantly different from the null value. In the PQDCS (1998-2000), radiologists' individual reading volumes were not associated with the detection rate, nor with the rate of interval cancers ≤ 12 months post-screen. Elsewhere, the literature is not unanimous on this point. In some cases, individual reading volume has been associated with measured performance, either in terms of sensitivity/specificity or cancer detection and referral for investigation, which represent an approximation of sensitivity/specificity, or in terms of the overall accuracy of screening, which is to say the capacity to correctly classify individuals who have/do not have cancer (58-65). Most of the studies that demonstrate a link between volume and performance have not taken into account the simultaneous effect of professionals and screening centres, although this seems essential if one is to make valid inferences concerning each of these factors.

Moreover, both cancer detection and the rate of interval cancers are influenced by screening centre volume. In earlier studies of the PQDCS evaluation team, the breast cancer detection rate was associated with screening centre volume, but not with the individual reading volume of radiologists (19,58). The present analysis shows that interval cancer rates decline with increasing screening centre volume.

Several factors may explain the superior performance of larger screening centres. Since the statistical models used here take several characteristics of women and radiologists into account, this relationship is not due to differences with respect to these factors between high volume and low volume centres. It is possible, however, that other attributes of the clientele/radiologists—attributes that exert an influence on frequency or cancer detection potential but which have not been measured in this study—may be responsible for these associations. Moreover, the technical aspects of screening mammography (which include

factors that are potentially critical from the standpoint of performance, such as image quality in the context of daily operations, centre-specific quality control procedures, and the expertise of technical personnel) are likely to vary from centre to centre, particularly in relation to screening volume. Such factors were not taken into account in this study. The importance of technical factors in the appropriate performance of screening mammography is generally recognized. Taplin and colleagues (66), for example, have demonstrated the marked reduction in mammographic sensitivity (84% to 66%) that occurs when breast positioning is incorrect. Nonetheless, studies that have attempted to put these factors and other determinants of quality into perspective are lacking. The evaluation team believes that this is an important area of research and intervention; specific studies to address these issues will be undertaken in the coming months.

In conclusion, the frequency of interval cancer in the PQDCS (1998-2000) is comparable to that observed in other screening programs and meets the requirements set out by the Evaluation Indicators Working Group, which monitors breast cancer screening programs in Canada. What is more, breast density greatly limits the capacity of screening mammography to detect cancer. This link between high breast density and reduced mammographic sensitivity has been observed in other studies and now represents the consensus view. Studies now underway in the United States and Europe should, in the coming years, help to identify measures to improve screening performance for women with very dense breasts. Finally, increased screening centre volume is linked to a higher detection rate and a lower rate of interval cancer in the first year post-screen. These observations suggest that screening sensitivity increases with screening centre volume. It is important to understand the reasons behind this link, so that all centres can benefit from the advantages offered by centres with a larger screening volume.

Table 1: Interval cancers following a normal initial mammogram - PQDCS 1998-2000

	Months from screening to diagnosis		
	≤ 24	**≤ 12**	**13-24**
Rate of DCIS and invasive interval cancers in women aged (/10,000 woman-years):			
50-54 years	11.3 (9.7-12.8)	6.3 (4.8-7.9)	17.6 (14.7-20.4)
55-59 years	13.0 (11.1-14.9)	7.4 (5.5-9.3)	20.0 (16.5-23.5)
60-64 years	13.2 (11.0-15.4)	7.8 (5.5-10.0)	20.0 (15.9-24.0)
65-69 years	15.1 (12.6-17.7)	7.5 (5.1-10.0)	24.3 (19.5-29.1)
50-69 years	**12.8 (11.8-13.8)**	**7.1 (6.1-8.1)**	**19.9 (18.1-21.7)**
Rate of invasive interval cancers in women aged (/10,000 woman-years):			
50-54 years	10.0 (8.5-11.4)	5.7 (4.2-7.2)	15.3 (12.6-18.0)
55-59 years	12.1 (10.3-13.9)	7.1 (5.2-9.0)	18.2 (14.9-21.6)
60-64 years	12.4 (10.3-14.6)	7.1 (4.9-9.3)	19.1 (15.1-23.1)
65-69 years	13.1 (10.8-15.5)	6.1 (3.9-8.3)	21.6 (17.1-26.1)
50-69 years	**11.6 (10.7-12.5)**	**6.4 (5.5-7.4)**	**18.0 (16.3-19.7)**

Table 2: Clinical characteristics of screening-detected cancers and interval cancers following a normal mammogram (initial mammogram) – PQDCS 1998-2000

	Screening-detected cancers	Interval cancers		
		Months from screening to diagnosis		
		≤ 24	≤ 12	13-24
	n=1,699 n (%)	n=569 n (%)	n=165 n (%)	n=404 n (%)
Type of cancer				
Invasive	1,307 (79.0)	515 (92.6)	150 (94.9)	365 (91.7)
In situ	348 (21.0)	41 (7.4)	8 (5.1)	33 (8.3)
Not known	44	13	7	6
Characteristics of invasive tumors				
Tumor size (cm)				
≤ 1.0	493 (43.7)	78 (21.5)	17 (21.2)	61 (21.6)
11.-1.5	334 (29.6)	88 (24.2)	13 (16.3)	75 (26.5)
1.6-2.0	126 (11.2)	77 (21.2)	20 (25.0)	57 (20.1)
> 2.0	174 (15.4)	120 (33.1)	30 (37.5)	90 (31.8)
Not known	180	152	70	82
Average size (cm)	1.39	2.05	2.30	1.98
Number of ganglia invaded				
0	700 (74.8)	201 (57.4)	37 (48.7)	164 (59.9)
1-3	175 (18.7)	92 (26.3)	21 (27.6)	7 (25.9)
4+	61 (6.5)	57 (16.3)	18 (23.7)	39 (14.2)
Not known	371	165	74	91
Histological type				
Canalar	917 (78.6)	303 (77.5)	65 (73.9)	238 (78.6)
Lobular	103 (8.8)	54 (13.8)	17 (19.3)	37 (12.2)
Tubular	84 (7.2)	10 (2.6)	3 (3.4)	7 (2.3)
Other	63 (5.4)	24 (6.1)	3 (3.4)	21 (6.9)
Not known	140	124	62	62
Histological grade				
I	438 (42.1)	92 (27.1)	20 (27.0)	72 (27.2)
II	453 (43.5)	131 (38.6)	26 (35.1)	105 (39.6)
III	150 (14.4)	116 (34.2)	28 (37.8)	88 (33.2)
Non evaluable/not known	266	176	76	100
Vascular invasion				
Present	177 (20.7)	132 (40.9)	30 (42.9)	102 (40.3)
None observed	680 (79.3)	191 (59.1)	40 (57.1)	151 (59.7)
Not known	450	192	80	112

Table 3: Description of women with screening-detected breast cancer, with interval cancer following a normal mammogram, and without breast cancer – PQDCS 1998-2000

		Women with cancer			Controls
		Screening-detected	Interval		
			Months from screening to diagnosis		
			≤ 12	13-24	
		n=1,699	n=165	n=404	n=48,200
Age	50-54	474 (27.9)	48 (29.1)	126 (31.2)	16,778 (34.8)
	55-59	434 (25.6)	46 (27.9)	111 (27.5)	12,911 (26.8)
	60-64	395 (23.2)	39 (23.6)	78 (19.3)	9,908 (20.6)
	65-69	396 (23.3)	32 (19.4)	89 (22.0)	8,603 (17.8)
Age at first childbirth	Nulliparous	369 (21.8)	27 (16.5)	85 (21.1)	7,512 (15.6)
	< 20	149 (8.8)	13 (7.9)	27 (6.7)	5,205 (10.8)
	20-24	580 (34.2)	67 (40.9)	136 (33.7)	19,726 (41.0)
	25-29	398 (23.5)	39 (23.8)	100 (24.8)	11,143 (23.2)
	30-34	152 (9.0)	15 (9.1)	41 (10.2)	3,426 (7.1)
	≥ 35	46 (2.7)	3 (1.8)	14 (3.5)	1,043 (2.2)
	Not known	5	1	1	145
Menopausal status	pre-menop.	181 (10.7)	15 (9.1)	38 (9.4)	5,694 (11.8)
	post-menop.	1,518 (89.3)	150 (90.9)	366 (90.6)	42,506 (88.2)
Family history	No	1,388 (82.6)	134 (82.2)	281 (70.6)	41,118 (86.2)
	Yes	292 (17.4)	29 (17.8)	117 (29.4)	6,583 (13.8)
	Not known	19	2	6	499
Hormone replacement therapy	Never	747 (44.0)	54 (32.7)	132 (32.7)	19,538 (40.5)
	In the past	131 (7.7)	8 (4.9)	15 (3.7)	3,965 (8.3)
	Currently	821 (48.3)	103 (62.4)	257 (63.6)	24,697 (51.2)
Body mass index (kg/m^2)	< 20.0	77 (4.5)	10 (6.1)	30 (7.4)	2,838 (5.9)
	20.0-24.9	637 (37.6)	81 (49.1)	192 (47.5)	19,579 (40.8)
	25.0-29.9	600 (35.4)	57 (34.5)	111 (27.5)	16,117 (33.6)
	30.0-34.9	265 (15.7)	11 (6.7)	48 (11.9)	6,669 (13.9)
	≥ 35.0	114 (6.7)	6 (3.6)	23 (5.7)	2,798 (5.8)
	Not known	6	0	0	199
Proportion of breast with density	< 25%	386 (22.7)	14 (8.5)	77 (19.1)	15,754 (32.7)
	25-49%	690 (40.6)	48 (29.1)	121 (29.9)	17,536 (36.4)
	50-75%	512 (30.1)	76 (46.1)	154 (38.1)	11,881 (24.7)
	> 75%	111 (6.6)	27 (16.4)	52 (12.9)	3,029 (6.3)

Table 3: Description of women with screening-detected breast cancer, with interval cancer following a normal mammogram, and without breast cancer – PQDCS 1998-2000 (continued)

		Women with cancer			Controls
		Screening-detected	Interval		
			Months from screening to diagnosis		
			≤ 12	13-24	
		n=1,699	n=165	n=404	n=48,200
Prior mammography	Yes	1,394 (82.0)	151 (91.5)	371 (91.8)	42,689 (88.6)
	No	305 (18.0)	14 (8.5)	33 (8.2)	5,511 (11.4)
Clinical breast examination	No	561 (33.0)	47 (28.5)	97 (24.0)	13,618 (28.3)
	Yes	1,138 (67.0)	118 (71.5)	307 (76.0)	34,582 (71.7)
History of puncture/biopsy	No	1,495 (88.0)	137 (83.0)	343 (84.9)	44,015 (91.3)
	Yes	204 (12.0)	28 (17.0)	61 (15.1)	4,185 (8.7)
Breast reduction	No	1,674 (98.5)	162 (98.2)	397 (98.3)	46,792 (97.1)
	Yes	25 (1.5)	3 (1.8)	7 (1.7)	1,408 (2.9)

Table 4: Odds ratios for screening-detected cancers and interval cancers following a normal mammogram, according to the characteristics of participants - PQDCS 1998-2000

		Screening-detected cancers		Interval cancers			
				Months from screening to diagnosis			
		(n=1,699)		≤ 12 (n=165)		13-24 (n=404)	
		Adjusted rate ratio*	(CI 95%)	Adjusted rate ratio*	(CI 95%)	Adjusted rate ratio*	(CI 95%)
Age	50-54	1.00		1.00		1.00	
	55-59	1.29	(1.13-1.47)	1.31	(0.91-1.90)	1.14	(0.87-1.49)
	60-64	1.53	(1.32-1.77)	1.61	(1.05-2.48)	1.16	(0.85-1.59)
	65-69	1.76	(1.52-2.03)	1.75	(1.10-2.78)	1.64	(1.21-2.21)
Age at first childbirth	Nulliparous	1.00		1.00		1.00	
	< 20	0.64	(0.53-0.78)	0.99	(0.54-1.83)	0.60	(0.39-0.93)
	20-24	0.64	(0.55-0.73)	1.17	(0.77-1.78)	0.72	(0.54-0.95)
	25-29	0.78	(0.67-0.91)	1.17	(0.74-1.86)	0.90	(0.66-1.22)
	30-34	0.96	(0.79-1.17)	1.41	(0.80-2.49)	1.18	(0.81-1.71)
	≥ 35	0.91	(0.66-1.25)	0.85	(0.27-2.72)	1.26	(0.73-2.19)
Menopausal status	pre-menop.	1.00		1.00		1.00	
	post-menop.	1.03	(0.86-1.23)	1.25	(0.73-2.14)	1.10	(0.78-1.53)
Family history	No	1.00		1.00		1.00	
	Yes	1.30	(1.14-1.49)	1.26	(0.84-1.91)	2.45	(1.99-3.01)
Hormone replacement therapy	Never	1.00		1.00		1.00	
	In the past	0.88	(0.73-1.07)	0.65	(0.32-1.34)	0.55	(0.32-0.96)
	Currently	0.99	(0.88-1.11)	1.18	(0.82-1.72)	1.49	(1.18-1.88)
Body mass index (kg/m^2)	< 20.0	1.00		1.00		1.00	
	20.0-24.9	1.33	(1.08-1.64)	1.69	(0.86-3.35)	1.20	(0.80-1.79)
	25.0-29.9	1.67	(1.34-2.07)	1.93	(0.98-3.79)	1.04	(0.67-1.62)
	30.0-34.9	1.94	(1.55-2.43)	1.23	(0.53-2.86)	1.35	(0.84-2.17)
	≥ 35.0	2.19	(1.62-2.96)	2.20	(0.77-6.30)	1.85	(1.06-3.23)
Proportion of breast with density	< 25%	1.00		1.00		1.00	
	25-49%	1.71	(1.49-1.97)	3.19	(1.84 - 5.55)	1.41	(1.04-1.91)
	50-75	1.97	(1.69-2.30)	8.16	(4.47-14.88)	2.58	(1.91-3.48)
	> 75%	1.77	(1.41-2.22)	13.00	(6.79-24.89)	3.29	(2.26-4.79)
Prior mammography	Yes	1.00		1.00		1.00	
	No	1.81	(1.57-2.07)	0.95	(0.55-1.66)	0.94	(0.67-1.32)

Table 4: Odds ratios for screening-detected cancers and interval cancers following a normal mammogram, according to the characteristics of participants - PQDCS 1998‑2000 (continued)

		Screening-detected cancers		Interval cancers			
				Months from normal screen to diagnosis			
				≤ 12		13-24	
		(n=1,699)		(n=165)		(n=404)	
		Adjusted rate ratio*	(CI 95%)	Adjusted rate ratio*	(CI 95%)	Adjusted rate ratio*	(CI 95%)
Clinical breast examination	No	1.00		1.00		1.00	
	Yes	0.84	(0.75-0.94)	0.93	(0.65-1.32)	1.11	(0.88-1.40)
History of puncture/biopsy	No	1.00		1.00		1.00	
	Yes	1.41	(1.21-1.65)	1.64	(1.09-2.47)	1.52	(1.17-1.98)
Breast reduction	No	1.00		1.00		1.00	
	Yes	0.55	(0.36-0.82)	0.89	(0.22-3.56)	0.69	(0.33-1.46)

* Adjusted for the characteristics of participants, radiologists, and screening centres.

Table 5: Distribution of screening-detected cancers and interval cancers following a normal mammogram, according to the characteristics of radiologists and screening centres - PQDCS 1998-2000

		Women with cancer			Controls
		Screening-detected	Interval		
			Months from screening to diagnosis		
			≤ 12	13-24	
		n=1,699	n=165	n=404	n=48,200
Radiologist's detection rate (/1,000 women)	< 4.0	207 (12.2)	58 (35.2)	120 (29.7)	12,985 (26.9)
	4.0-5.9	491 (28.9)	52 (31.5)	128 (31.7)	16,000 (33.2)
	6.0-7.9	446 (26.2)	32 (19.4)	85 (21.0)	10,270 (21.3)
	≥ 8.0	555 (32.7)	23 (13.9)	71 (17.6)	8,945 (18.5)
Radiologist's false positive rate (%)	< 10.0	684 (40.2)	92 (55.7)	204 (50.5)	23,974 (49.7)
	10.0-14.9	600 (35.3)	46 (27.9)	132 (32.7)	15,914 (33.0)
	15.0-19.9	294 (17.3)	15 (9.1)	58 (14.4)	6,119 (12.7)
	≥ 20.0	120 (7.1)	11 (6.7)	9 (2.2)	2,095 (4.4)
	Non-applicable	1 (0.1)	1 (0.6)	1 (0.2)	98 (0.2)
Number of screening centres	1	705 (41.5)	71 (43.0)	183 (45.3)	20,835 (43.2)
	2	502 (29.6)	38 (23.0)	109 (27.0)	13,944 (28.9)
	3	339 (19.9)	36 (21.8)	79 (18.5)	9,403 (19.5)
	4 +	153 (9.0)	20 (12.1)	33 (8.2)	4,018 (8.3)
Type of screening centre	Radiology clinic	1,378 (81.1)	132 (80.0)	341 (84.4)	39,523 (82.0)
	Hospital	321 (18.9)	33 (20.0)	63 (15.6)	8,677 (18.0)
Radiologist's reading volume	1-499	408 (24.0)	38 (23.0)	93 (23.1)	10,537 (21.9)
	500-749	441 (26.0)	44 (26.7)	108 (26.7)	13,221 (27.4)
	750-999	359 (21.1)	40 (24.2)	78 (19.3)	10,092 (20.9)
	1,000-1,249	211 (12.4)	16 (9.7)	55 (13.6)	6,209 (12.9)
	1,250-1,499	150 (8.8)	11 (6.7)	42 (10.4)	3,919 (8.1)
	≥ 1,500	130 (7.7)	16 (9.7)	28 (6.9)	4,222 (8.8)
Centre's screening volume	< 2,000	395 (23.2)	46 (27.9)	87 (21.5)	12,577 (26.1)
	2,000-2,999	602 (35.4)	70 (42.4)	150 (37.1)	18,118 (37.6)
	3,000-3,999	351 (20.7)	30 (18.2)	101 (25.0)	10,020 (20.8)
	≥ 4,000	351 (20.7)	19 (11.5)	66 (16.3)	7,485 (15.5)

Table 6: Odds ratios of screening-detected cancers and interval cancers following a normal mammogram, according to the characteristics of radiologists and screening centres - PQDCS 1998-2000

		Screening-detected cancers		Interval cancers			
				Months from normal screen to diagnosis			
		(n=1,699)		≤ 12 (n=165)		13-24 (n=404)	
		Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)
Radiologist's detection rate (/1,000 women)	< 4.0	1.00		1.00		1.00	
	4.0-5.9	1.86	(1.67-2.07)	0.81	(0.52-1.28)	0.85	(0.67-1.09)
	6.0-7.9	2.54	(2.26-2.85)	0.77	(0.47-1.24)	0.94	(0.72-1.22)
	≥ 8.0	3.54	(3.14-3.98)	0.67	(0.39-1.12)	0.87	(0.64-1.18)
Radiologist's false positive rate (%)	< 10.0	1.00		1.00		1.00	
	10.0-14.9	1.08	(1.00-1.17)	0.79	(0.53-1.19)	1.09	(0.88-1.34)
	15.0-19.9	1.08	(0.96-1.22)	0.78	(0.42-1.46)	1.44	(1.05-1.98)
	≥ 20.0	1.31	(1.11-1.54)	1.44	(0.61-3.36)	0.59	(0.32-1.11)
Number of screening centres	1	1.00		1.00		1.00	
	2	1.07	(0.99-1.16)	0.81	(0.53-1.24)	0.97	(0.76-1.23)
	3	1.06	(0.97-1.17)	1.09	(0.71-1.69)	1.11	(0.85-1.45)
	4 +	1.04	(0.91-1.18)	1.49	(0.93-2.39)	1.17	(0.79-1.71)
Type of screening centre	Radiology clinic	1.00		1.00		1.00	
	Hospital	0.98	(0.88-1.09)	0.94	(0.59-1.50)	0.76	(0.57-1.01)
Radiologist's reading volume†	1-499	1.00		1.00		1.00	
	500-749	0.91	(0.79-1.05)	0.92	(0.60-1.42)	0.82	(0.63-1.07)
	750-999	0.95	(0.81-1.12)	1.23	(0.75-2.01)	0.81	(0.60-1.09)
	1,000-1,249	0.90	(0.78-1.05)	0.92	(0.56-1.53)	0.95	(0.68-1.32)
	1,250-1,499	0.95	(0.77-1.16)	1.00	(0.46-2.18)	0.88	(0.61-1.26)
	≥ 1,500	0.96	(0.74-1.25)	1.16	(0.58-2.36)	0.60	(0.41-0.87)
Centre's screening volume†	< 2,000	1.00		1.00		1.00	
	2,000-2,999	1.04	(0.91-1.19)	1.11	(0.75-1.63)	1.28	(1.02-1.61)
	3,000-3,999	1.25	(1.05-1.48)	0.77	(0.48-1.25)	1.41	(1.06-1.88)
	≥ 4,000	1.41	(1.15-1.72)	0.63	(0.37-1.06)	1.09	(0.78-1.53)

* Adjusted for the characteristics of participants, radiologists, and screening centres.

† Odds ratios adjusted for the characteristics of participants, radiologists and screening centres, with the exception of the *radiologist's detection rate*.

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APPENDIX 1

PROCEDURE FOR THE IDENTIFICATION OF INTERVAL CANCERS SUBSEQUENT TO A NORMAL INITIAL MAMMOGRAM, PQDCS

APPENDIX 1: PROCEDURE FOR THE IDENTIFICATION OF INTERVAL CANCERS SUBSEQUENT TO A NORMAL INITIAL MAMMOGRAM, PQDCS

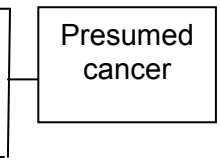
A selection is made from among the screening data found in the program's information system (SI-PQDCS). Mammograms with a normal result, carried out in 1998, 1999 and 2000 with women who were 50 to 69 years of age at the time of the examination are extracted from the system. In the case of women who had more than one mammographic examination, the information pertaining to subsequent mammographies is used to identify and eliminate women whose cancer was detected at a recall examination rather than an initial screen. The vast majority of the women had a single normal mammogram during the period. A smaller number had had two mammograms, and a few had had three. The information retained on the women consisted of unique variables that were usable for the purposes of matching: date of birth, date of mammography, place of residence, where the mammography was performed (all of which are variables that are likely to differ), as well as a number of indicator variables. These data are then matched up with MedÉcho data with the aid of health insurance numbers. MedÉcho records contain information on discharge dates (first date retained, between May 1, 1998 and December 31, 2001), the facility, the hospital record number, and the behaviour and morphology of the tumor. If, for a single discharge date, a diagnosis of invasive cancer and a second diagnosis of *in situ* cancer are found, the invasive cancer is retained. If a woman was screened more than once during the period, the cancer is associated with the nearest screening date preceding the discharge date. Subsequently, a second extraction is carried out from the screening records to identify those women who had a mammography that produced an abnormal result on a subsequent episode (second or later) during the period in question. These data are matched with the normal mammogram data. The goal is to determine whether an abnormal mammogram occurred between a normal mammogram and the date of the cancer. If so, the cancer is more likely to be linked to the abnormal mammogram. In order to verify this, a further extraction is carried out for screening data falling between January 1, 2001 and June 30, 2002. This time, the goal is to determine whether there was a normal or abnormal mammogram between a normal mammogram from the period and a cancer with a date that falls outside the period. Once the normal mammographies from the period that have a direct and unique link with a cancer have been identified, the record of procedures of the *Régie de l'assurance maladie du Québec* (RAMQ) can be analysed.

A record is obtained from RAMQ for every woman who received a normal mammogram report during the period under review. This record contains all breast-related procedures (see attached list) carried out between May 1, 1998 and December 31, 2001. It also contains personal identifiers, the place of residence, procedure codes, procedure dates, and the place where the procedure was carried out. Matching is done using the health insurance number. The first stage consists of matching screening dates in the SI-PQDCS with screening dates in the RAMQ records (all procedures in RAMQ records that occurred prior to the period are eliminated). Given the fairly complex nature of this matching process, which is based on multiple occurrences in the PQDCS information system and multiple occurrences in RAMQ records, and in view of the fact that a large number of procedure dates do not coincide exactly, matching will be carried out using discreet segments of data from the SI-PQDCS. For example, the vast majority of the women had one screen in the SI; this sub-record will be

treated individually. Subsequently, if a woman has two mammograms, the first will be analysed individually, with follow-up stopping at the date of the second mammogram. The second mammogram will then be synchronized individually with RAMQ procedures, in order to ascertain the sequence of procedures. Procedures that took place before the second mammogram are eliminated, since they have already been matched to the first mammogram. This synchronization is important in order to avoid counting two mammographies that appear to have occurred close in time, since these are likely due to billing date errors. Once the RAMQ records have been adjusted correctly, the procedures are summarized into categories of severity (see below) comprising a single procedure or a group of procedures, based on worst-case scenarios. For example, “no more than one core biopsy or no more than one breast surgery with adjuvant treatment.” Certain categories, such as the latter, represent a validated and almost certain indicator of cancer. RAMQ records are therefore made to serve two functions: to find other cases of cancer that have not been identified in MedÉcho, and to ensure that there are no other mammograms which the SI failed to identify between a normal mammogram from the period under review and the date of the cancer. These might be screening mammograms of non-participants or a diagnostic mammogram (for annual follow-up purposes, diagnostic mammography is frequently carried out between two biennial screening mammographies; since November 2001, women can now receive annual mammography by medical prescription). In order to verify this last point, the RAMQ records are transformed so that all the data are on the same line.

RAMQ categories

Screening only	1
Diagnostic mammography, ultrasound or other radiological investigation only	2
Cytological puncture only	3
Guided biopsy only	4
Guided biopsy **and** adjuvant therapy only	5
Mastectomy or axillary dissection **and** adjuvant treatment only	6
Open biopsy only	7
Mastectomy or axillary dissection only	8
Open biopsy **and** adjuvant treatment only	9



CATEGORIZATION OF MAMMOGRAPHY, DIAGNOSTIC CONFIRMATION AND SURGICAL TREATMENT PROCEDURES OBTAINED FROM RAMQ

Procedure code	Description of procedure[1]
Screening mammography	
8079	Bilateral screening mammography (50-69 years)
8134	Selective screening mammography for women aged 40 to 49 years or 70 and over, unilateral (V-16)
8135	Selective screening mammography for women aged 40 to 49 years or 70 and over, bilateral (V-16)
8145	Unilateral screening mammography (mobile mammography unit)(V-17)
8146	Bilateral screening mammography (mobile mammography unit)(V-17)
Diagnostic mammography	
8078	Unilateral screening mammography (50-69 years)
8048	Diagnostic mammography without clinical examination, unilateral
8049	Diagnostic mammography without clinical examination, bilateral
8070	Diagnostic mammography with clinical examination, unilateral
8071	Diagnostic mammography with clinical examination, bilateral
8140	Mammography without clinical examination, unilateral
8141	Mammography without clinical examination, bilateral
8142	Mammography with clinical examination performed by radiologist and progress notes recorded, unilateral
8143	Mammography with clinical examination performed by radiologist and progress notes recorded, bilateral
8089	Systematic screening mammography (for women aged 50 to 69, additional views (old code)
8103	Systematic screening mammography (for women aged 50 to 69), additional views: unilateral
8104	Systematic screening mammography (for women aged 50 to 69), additional views: bilateral
8137	Selective screening mammography (for women aged 40 to 49 or 70 and over), additional views (V-16)
Ultrasound	
8333	Breast surface ultrasound, per breast

[1] Manuel des médecins spécialistes, Régie de l'assurance maladie du Québec, Service des communications (Publications), Quebec, 2001.

CATEGORIZATION OF MAMMOGRAPHY, DIAGNOSTIC CONFIRMATION AND SURGICAL TREATMENT PROCEDURES OBTAINED FROM RAMQ (CONTINUED)

Procedure code	Description of procedure[1]
Other radiological examinations	
0442	Injection of contrast medium: Galactography
0444	Injection of contrast medium: breast cyst, including aspiration
8201	Galactography, including injection
8202	Cystography, including injection
8144	Review examination following abnormal screening mammogram: fees paid to a radiologist in a designated reference centre for examination (CRID) for evaluation of a file (examinations carried out in a DSC and previous films).
Fine needle puncture	
0594	Therapeutic drainage, including diagnostic specimen: breast cyst
0798	Breast biopsy (needle), one or more
1011	Incision: drainage of breast abscess, single or multilocular (F-11)
0847	Puncture of breast cyst with aspiration under echography or stereotaxic guidance including, if necessary, injection of air and/or post-puncture mammography
0848	Puncture and/or biopsy of palpable or non-palpable breast lump using fine-needle aspiration under echography or stereotaxic guidance, including a follow-up mammography if necessary
9470	Needle biopsy/cytology via transcutaneous route, under echographic, fluoroscopic or scanographic guidance: localization or biopsy of a palpable breast lump, or both
Guided biopsy	
0551	Biopsy of a non-palpable breast lump with a dedicated device (cross-hatched breast compression plate or stereotaxic device), including mammography performed the same day, if necessary
0561	Localization of a non-palpable breast lump with a dedicated device (cross-hatched breast compression plate or stereotaxic device), including post-localization mammography and biopsy, if necessary
1202	Excisional stereotaxic breast biopsy, including the entire technical procedure (ABBI)

[1] Manuel des médecins spécialistes, Régie de l'assurance maladie du Québec, Service des communications (Publications), Quebec, 2001.

CATEGORIZATION OF MAMMOGRAPHY, DIAGNOSTIC CONFIRMATION AND SURGICAL TREATMENT PROCEDURES OBTAINED FROM RAMQ (CONTINUED)

Procedure code	Description of procedure[1]
0849	Core biopsy of a palpable or non-palpable breast lump with core tissue sampling under echography or stereotaxic guidance, including a follow-up mammography if necessary
Open biopsy	
1173	Breast (excision): multiple biopsy of the breast (breast, internal mammary nodes, axilla, etc.)
1174	Breast (excision): tumor or tissue fragment for single or multiple biopsy
1175	Removal of a cyst, fibroadenoma (or other benign tumor in abnormal breast tissue), or lesion of the excretory canal or nipple, including all other partial mastectomies in women or men
1201	Excision of benign lesion/core tissue
1203	Tumorectomy or partial mastectomy for benign lesion
1204	Tumorectomy or partial mastectomy for malignant lesion
1205	Tumorectomy or partial mastectomy for benign or malignant lesion (replaced 1203-1204 in April 2001)
1229	Partial mastectomy
Breast cancer-related treatments	
1228	Partial mastectomy with radical dissection of axilla
1230	Simple or total mastectomy
1231	Radical or modified radical mastectomy
1232	Radical mastectomy with excision of internal mammary nodes
1235	Excision of nipple
4240	Dissection of axillary lymph nodes
4199	Exeresis of one or more sentinel nodes at same site, including the entire identification and localization procedure but excluding radical dissection
8538	Brachytherapy (breast)
Adjuvant treatments	
0734	Intravenous chemotherapy (injection of one or more antineoplastic substances)

[1] Manuel des médecins spécialistes, Régie de l'assurance maladie du Québec, Service des communications (Publications), Quebec, 2001.

CATEGORIZATION OF MAMMOGRAPHY, DIAGNOSTIC CONFIRMATION AND SURGICAL TREATMENT PROCEDURES OBTAINED FROM RAMQ (CONTINUED)

Procedure code	Description of procedure[1]
8511	Planning radiation treatment of non-cutaneous lesions
8553	Planning radiation treatment of non-cutaneous lesions with computerized axial tomography

[1] Manuel des médecins spécialistes, Régie de l'assurance maladie du Québec, Service des communications (Publications), Quebec, 2001.

APPENDIX 2

DESCRIPTION OF THE CHARACTERISTICS OF INTERVAL CANCERS FOLLOWING A NORMAL INITIAL MAMMOGRAM

APPENDIX 2: DESCRIPTION OF THE CHARACTERISTICS OF INTERVAL CANCERS FOLLOWING A NORMAL INITIAL MAMMOGRAM

1. The type of cancer is determined using the strategy described in the report entitled "*Validation de stratégies pour obtenir le taux de détection du cancer, la valeur prédictive positive, la proportion des cancers in situ, la proportion des cancers infiltrants de petite taille et la proportion des cancers infiltrants sans envahissement ganglionnaire dans le cadre des données fournies par le Programme québécois de dépistage du cancer du sein* (PQDCS)" [validation of strategies to ascertain cancer detection rates, positive predictive values, the proportion of *in situ* cancers, the proportion of small invasive cancers, and the proportion of invasive cancers without node invasion, based on data provided by the Quebec Breast Cancer Screening Program (PQDCS)] (32). This strategy uses all of the data found in the PQDCS information system and, in the case of cancers for which no information is present in the PQDCS information system, the data from MedÉcho records. For interval cancers, we use the cancer type provided in MedÉcho (rather than the pathology reports received).

2. Tumor size and lymph node invasion are determined using the strategy described in the same report. This strategy uses all of the information found in the PQDCS information system and, in the case of cancers for which no information is present in the PQDCS information system, the data from available pathology reports. For interval cancers, pathology reports are necessarily used.

Example:

Women	**A**	**B**
MedÉcho	**Invasive**	***In situ***
Pathology report	*In situ* Tumor size and lymph node invasion are a missing value, since this cancer is identified as an invasive cancer (according to the strategy), but the pathology report refers to it as an *in situ* tumor.	Invasive Tumor size and lymph node invasion are present in the pathology report but will not be used since this cancer is identified as *in situ* (according to the strategy).

3. For the other cancer characteristics, the information from the pathology reports is used.

APPENDIX 3

ADDITIONAL DATA

APPENDIX 3: ADDITIONAL DATA

Table 7: Odds ratios of invasive cancers detected by screening and invasive interval cancers following a normal mammogram, based on the characteristics of participants, PQDCS 1998-2000

		Screening-detected cancers		Interval cancers			
				Months between normal screen and diagnosis			
				≤ 12		13-24	
		Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)
Age	50-54	1.00		1.00		1.00	
	55-59	1.35	(1.16-1.58)	1.41	(0.96-2.05)	1.24	(0.93-1.64)
	60-64	1.72	(1.46-2.03)	1.67	(1.07-2.60)	1.32	(0.94-1.84)
	65-69	2.01	(1.71-2.36)	1.68	(1.02-2.76)	1.80	(1.32-2.46)
Age at first childbirth	Nulliparous	1.00		1.00		1.00	
	< 20	0.72	(0.58-0.89)	0.85	(0.44-1.65)	0.64	(0.41-1.01)
	20-24	0.68	(0.58-0.80)	1.04	(0.68-1.59)	0.77	(0.57-1.05)
	25-29	0.78	(0.65-0.94)	1.13	(0.72-1.79)	0.90	(0.64-1.25)
	30-34	1.00	(0.80-1.26)	1.14	(0.61-2.14)	1.26	(0.85-1.89)
	≥ 35	1.03	(0.72-1.48)	0.86	(0.27-2.74)	1.45	(0.83-2.52)
Menopausal status	Pre-menop.	1.00		1.00		1.00	
	Post-menop.	1.06	(0.87-1.30)	1.17	(0.67-2.02)	1.01	(0.70-1.45)
Family history	No	1.00		1.00		1.00	
	Yes	1.28	(1.10-1.49)	1.29	(0.84-1.99)	2.37	(1.88-2.97)
Hormone replacement therapy	Never	1.00		1.00		1.00	
	In the past	0.80	(0.64-1.01)	0.76	(0.37-1.60)	0.55	(0.32-0.96)
	Currently	1.01	(0.89-1.15)	1.28	(0.86-1.89)	1.58	(1.24-2.03)
Body mass index (kg/m^2)	< 20.0	1.00		1.00		1.00	
	20.0-24.9	1.40	(1.07-1.84)	1.77	(0.86-3.65)	1.11	(0.74-1.68)
	25.0-29.9	1.79	(1.37-2.35)	1.98	(0.97-4.00)	0.99	(0.63-1.57)
	30.0-34.9	2.16	(1.64-2.86)	1.18	(0.46-3.05)	1.20	(0.73-1.95)
	≥ 35.0	2.41	(1.67-3.46)	2.58	(0.88-7.51)	1.77	(1.00-3.13)
Proportion of breast with density	< 25%	1.00		1.00		1.00	
	25-49%	1.65	(1.41-1.92)	2.82	(1.58 - 5.03)	1.39	(1.02-1.90)
	50-75%	1.83	(1.54-2.17)	7.96	(4.24-14.94)	2.61	(1.93-3.55)
	> 75%	1.50	(1.14-1.98)	12.91	(6.55-25.45)	3.41	(2.33-5.00)
Prior mammography	Yes	1.00		1.00		1.00	
	No	1.81	(1.55-2.12)	0.76	(0.40-1.44)	0.97	(0.67-1.38)

Table 7: Odds ratios of invasive cancers detected by screening and invasive interval cancers following a normal mammogram, based on the characteristics of participants, PQDCS 1998-2000 (continued)

		Screening-detected cancers		Interval cancers			
				Months from normal screen to diagnosis			
				≤ 12		13-24	
		Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)
Clinical breast examination	No	1.00		1.00		1.00	
	Yes	0.81	(0.72-0.91)	0.89	(0.61-1.31)	1.14	(0.89-1.45)
History of puncture/biopsy	No	1.00		1.00		1.00	
	Yes	1.40	(1.17-1.67)	1.70	(1.12-2.60)	1.44	(1.09-1.89)
Breast reduction	No	1.00		1.00		1.00	
	Yes	0.59	(0.37-0.93)	0.96	(0.24-3.82)	0.77	(0.36-1.64)

* Adjusted for the characteristics of participants, radiologists, and screening centres.

Table 8: Odds ratios of invasive cancers detected by screening and invasive interval cancers following a normal mammogram, based on the characteristics of the radiologists and screening centres, PQDCS 1998-2000

		Screening-detected cancers		Interval cancers			
				Months from normal screen to diagnosis			
				≤ 12		13-24	
		Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)	Adjusted odds ratio*	(CI 95%)
Radiologist's detection rate (/1,000 women)	< 4.0	1.00		1.00		1.00	
	4.0-5.9	1.79	(1.55-2.06)	0.73	(0.44-1.20)	0.84	(0.64-1.11)
	6.0-7.9	2.40	(2.08-2.76)	0.64	(0.38-1.08)	1.01	(0.77-1.32)
	≥ 8.0	3.41	(2.93-3.97)	0.64	(0.37-1.12)	0.84	(0.60-1.18)
Radiologist's false positive rate (%)	< 10.0	1.00		1.00		1.00	
	10.0-14.9	1.15	(1.05-1.27)	0.75	(0.48-1.17)	0.95	(0.77-1.19)
	15.0-19.9	1.08	(0.94-1.24)	0.72	(0.37-1.40)	1.36	(0.99-1.86)
	≥ 20.0	1.30	(1.04-1.62)	1.21	(0.51-2.89)	0.50	(0.26-0.97)
Number of screening centres	1	1.00		1.00		1.00	
	2	1.09	(0.99-1.20)	0.74	(0.47-1.16)	0.94	(0.72-1.22)
	3	1.08	(0.96-1.21)	1.00	(0.63-1.61)	0.96	(0.71-1.30)
	4+	0.99	(0.83-1.19)	1.42	(0.88-2.29)	1.18	(0.81-1.73)
Type of screening centre	Radiology clinic	1.00		1.00		1.00	
	Hospital	0.94	(0.83-1.07)	0.91	(0.56-1.49)	0.78	(0.58-1.05)
Radiologist's reading volume†	1-499	1.00		1.00		1.00	
	500-749	0.87	(0.74-1.02)	0.95	(0.60-1.53)	0.83	(0.63-1.10)
	750-999	0.92	(0.78-1.10)	1.19	(0.70-2.03)	0.80	(0.57-1.12)
	1,000-1,249	0.92	(0.79-1.08)	0.89	(0.51-1.54)	0.93	(0.66-1.32)
	1,250-1,499	0.91	(0.75-1.12)	1.15	(0.51-2.58)	0.90	(0.62-1.29)
	≥ 1,500	0.95	(0.75-1.22)	1.26	(0.61-2.57)	0.53	(0.36-0.78)
Centre's screening volume†	< 2,000	1.00		1.00		1.00	
	2,000-2,999	1.02	(0.88-1.18)	1.10	(0.73-1.65)	1.20	(0.93-1.53)
	3,000-3,999	1.29	(1.07-1.55)	0.67	(0.39-1.15)	1.20	(0.87-1.64)
	≥ 4,000	1.37	(1.11-1.68)	0.70	(0.41-1.19)	1.05	(0.75-1.47)

* Adjusted for the characteristics of participants, radiologists, and screening centres.

† Odds ratios adjusted for the characteristics of participants, radiologists and screening centres, except for the *radiologist's detection rate*.

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