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Ataxia-Telangiectasia genes and breast cancer risk in a French family study

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Ataxia-telangiectasia (AT) is a rare autosomal recessive early childhood disorder, characterized by progressive neuronal degeneration, immunological deficiency, radiosensitivity and an increased risk of cancer caused in most cases by mutations in the AT-mutated gene (*ATM*). Epidemiological studies on AT families have shown that AT heterozygous women have an increased risk of developing breast cancer (BC). The ATM protein plays a central role in the recognition and repair of DNA double-strand breaks and the subsequent activation of cell-cycle checkpoints. Whilst AT is a rare disease, 0·5–1% of the general population are estimated to be AT mutation carriers, thus any increases in the risks of cancer associated with *ATM* carrier status are of public health relevance. The main results of our published studies on the risk of BC in 34 French AT families according to heterozygote status, type of *ATM* mutation and exogenous factors are summarized here. The risk of BC was higher in *ATM* heterozygous (HetATM) women and did not differ significantly according to the type of *ATM* mutation (missense vs truncating) carried by the AT family members but appeared associated with the position of some truncating mutations in certain binding domains of the ATM protein. The effect of exogenous factors, such as reproductive life factors and exposure to ionizing radiation, on the risk of BC according to *ATM* heterozygote status was assessed. There was no evidence for interaction (except for age at first full-term pregnancy). These findings does not appear to justify a separate screening program from that already available to other women with a first-degree relative affected by BC, as their risks have similar amplitude. Chest X-rays did not appear to be a risk factor for BC in our study population. More powerful studies, using data sets pooled from international sources are being set up to confirm these observations.

Keywords: Ataxia-telangiectasia heterozygosis, breast cancer, family study.

Ataxia-telangiectasia (AT) is a rare autosomal recessive early childhood disorder, characterized by progressive neuronal degeneration, immunological deficiency, radiosensitivity and an increased risk of cancer. Epidemiological studies on AT families have shown that AT heterozygotes (HetAT) have an increased risk of developing cancer, particularly breast cancer (BC) in the female relatives. Swift (1976) and his collaborators were the first to publish results suggesting that HetAT may have an increase risk of cancer. They showed (Swift et al. 1976, 1987, 1991) that an increased relative risk (RR) of developing cancer in the male HetAT of 3·8 and in the female HetAT of 3·5. The RR of developing BC was estimated to be 5 (Swift et al. 1991). Two other studies in which AT family members were studied showed an increased RR of developing BC of 1·3 and 3·9 (Borresen et al. 1990; Pippard et al. 1988). Since 1996, five studies have been published which report similar risks of developing BC in HetAT (Athma et al. 1996; Stankovic et al. 1998; Inskip et al. 1999; Janin et al. 1999; Olsen et al. 2001).

The majority of AT cases are associated with mutations in the *ATM* (AT mutated) gene located on chromosome 11 (Savitsky et al. 1995a). The ATM protein plays a central

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role in the recognition and repair of DNA double-strand breaks and in the subsequent activation of cell-cycle checkpoints (Savitsky et al. 1995a, b).

Since the *ATM* gene was isolated (Savitsky et al. 1995a), BC cases and controls have been screened for *ATM* mutations. Indeed, whilst AT is a rare disease, 0·5–1% of the general population are estimated to be AT mutation carriers, thus any increases in the risks of cancer associated with *ATM* carrier status are of public health relevance. Many of the first case-control studies failed to find significant differences in the frequency of the *ATM* mutations between cases and controls (e.g. Vorechovsky et al. 1996a, b; FitzGerald et al. 1997; Chen et al. 1998). However it was noted that missense mutations were more frequently detected compared with truncating mutations than would have been expected based on their relative frequencies in AT patients. This apparent discrepancy between the findings of the familial studies and those of the case-control studies led authors to suggest that the two types of *ATM* heterozygosity may confer different cancer risks (McConville et al. 1996; Gatti et al. 1999; Meyn, 1999).

Although several studies have shown that AT heterozygosis increases the risk of BC, whether exogenous factors affected this risk has not been previously examined. Only Swift et al. (1987, 1991) have attempted to study the role of radiation exposure and found that the risk of developing BC was six-fold higher among women who had received X-rays from fluoroscopic procedures involving the chest or abdomen. Breast epithelium shows a rapid proliferation during puberty and under the influence of estrogenic hormones. Thus, like BRCA-deficient cells (Scully & Livingston, 2000), *ATM* heterozygous breast cells carrying the DNA repair deficiency remain immature for a more or less long period (e.g. from menarche to first childbirth, first three months of pregnancy etc.) leading to a potential hypersensitivity to genotoxic carcinogens. Thus, the risk of BC may vary according to reproductive factors and ionizing radiation.

In this paper, we review our published data on BC risk within the setting of French AT families. The risk of BC has been assessed among 34 families with AT children according to *ATM* heterozygote status, type of mutation and environment factors (Geoffroy-Perez et al. 2001, 2002; Cavaciuti et al. 2005).

Methods and Data Collection

A family study of AT children was carried out in France between June 1994 and February 1997. The main design feature of this study and the genotyping of the AT locus have been previously described (Janin et al. 1999) and are summarized below. AT children were recruited by paediatricians who have been surveying this population since early childhood, and cytogeneticists who have contributed to their disease diagnosis. For each participant a blood sample was taken; and a questionnaire was distributed by a physician to all adult relatives. A blood or a buccal cells sample was taken from the AT children and their siblings with parental agreement.

Demographic characteristics (gender, date of birth, and, if deceased, age at death and cause of death) and the occurrence of BC and any other cancer, including age at diagnosis and places of medical care were collected from first- to third-degree relatives. Epidemiological data on 175 first- and second-degree female relatives aged 18 years or over concerned medical history, exposures to medical and professional radiation and detailed reproductive factors and were collected during a face to face interview. 15 off the 28 women with BC were still alive at the time of the study and all agreed to participate.

The methods used for the identification of *ATM* germline mutations were modified as new techniques became available during the study period. For the AT patients from 24/34 families, eight overlapping cDNA fragments covering the whole coding sequence (62 coding exons) were obtained using RNA isolated from the corresponding lymphoblastoid cell line. An analysis of the size of the fragments was used to screen for the presence of any large partial deletions of the *ATM* gene. Smaller mutations were detected by restriction endonuclease fingerprinting (REF), the protein truncation test (PTT), fluorescent assisted mismatch assays (FAMA), or more recently direct sequencing. When a variant pattern was observed by REF, PTT, or FAMA, the cDNA was sequenced in both directions using DyeDeoxy Terminator Cycle sequencing kits (Applied Biosystems Inc.) using an ABI377 DNA sequencer or ABI PRISM 3100 Genetic Analyser (Applied Biosystems, Inc.). When an abnormal transcript was detected, the genomic DNA was analysed to identify the origin of the splicing defect. Since the end of 2003, the 62 coding exons and the intron-exon boundaries have been analysed by sequencing using the BigDye Terminator Cycle Sequencing V1.1 Ready Reaction kit (Applied Biosystems Inc.). SeqScape software was used for sequence analysis (Applied Biosystems, Inc.).

The parental origin of each mutation was determined by identifying the mutations in DNA samples from both the mother and father. When lymphoblastoid cell lines were unavailable for the AT children, *ATM* screening was performed on the parents. When no mutation was found, *ATM* heterozygosity was determined from the haplotypes. The haplotypes were established from the segregation pattern in the families using of markers closely linked to *ATM* (Janin et al. 1999). When *ATM* heterozygote status could not be determined, the probability that the individual shares an *ATM* mutation with his/her closest HetATM relative was calculated. As a result four classes of relatives were defined: relatives who were obligate-HetATM, relatives with a 0·5 probability of being an *ATM* carrier (50% HetATM), relatives with a 0·25 probability of being an *ATM* carrier (25% HetATM), and relatives that were not carriers (non HetATM). Siblings of the AT children for

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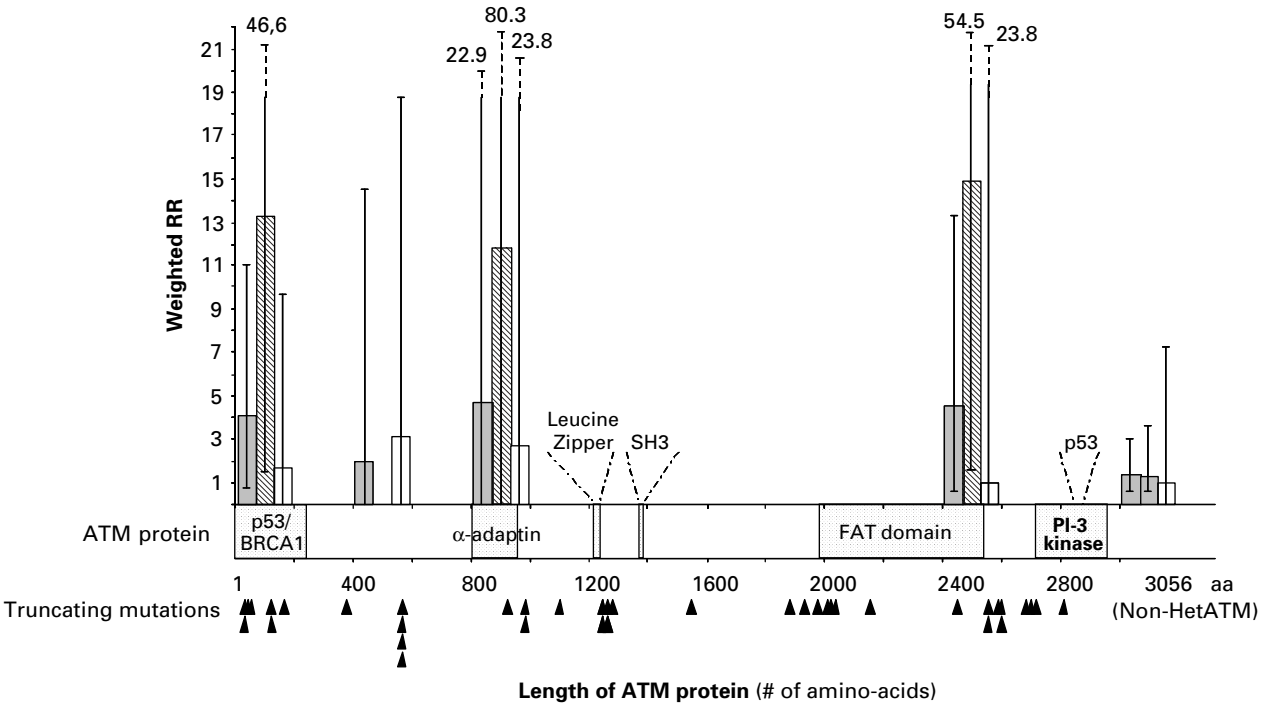

Fig. 1. Breast cancer risk according to the predicted length of ATM proteins resulting from truncating mutations from Cavaciuti et al. (2005). The relative risk and 95% CI are shown in dashed for women <45 years old, white for women ⩾45 years old and gray for all women. Black arrows indicate truncating mutations. For comparative purposes, the relative risks for the three age-groups of female relatives in the non HetATM group are shown Weighted RR is RR weighed on the *a priori* probability of being heterozygotes for *ATM*.

whom no DNA samples were available had a 0·66 probability of being HetATM, there were 6 sisters and they were included in the 50% HetATM category. Similarly, 15 subjects, for whom the probability of being heterozygote was 0·17 or less, were included in the non-HetATM group. None of these individuals were diagnosed with BC.

Relatives of AT children were considered at risk from birth until their age at interview or age at death (for subjects unaffected by cancer), or age at diagnosis (for subjects with cancer). When the age at diagnosis of cancer was unknown, age at death was used.

The expected number of breast cancers per 5-year age category was calculated from the French age-, sex- and period-specific (1978 to 1982, 1983 to 1987, 1988 to 1992) estimated incidences (Benhamou et al. 1990; De Vathaire et al. 1996; Ménégoz & Chérié-Challine, 1999), using the PYRS program (Coleman et al. 1986). The estimated incidences for the period 1978 to 1982 were used to calculate the expected number of BC in the period before 1978 and the estimated incidences for the period 1988 to 1992 were used to calculate the expected number of BC in the period after 1992. The RR of BC associated with HetATM status was estimated by the standardized incidence ratio (SIR), i.e. the ratio between the observed number of cases (O) and the expected number of cases (E) in the AT families. RR were adjusted on non-HetATM (RRadj) by dividing each SIR by the SIR of the non-HetATM group. We also calculated the RR weighed on the *a priori* probability of being HetATM (RR_w) according to Thompson & Easton (2002). Two-sided 95% confidence intervals (CIs) for RR estimates, heterogeneity and trend tests are based on the approximation of the Poisson distribution (Breslow & Day, 1987).

To assess the association of the location of the truncating mutations and BC risk, the ATM protein was arbitrarily divided into 15 sections, 14 of which contained 200 amino-acids (aa) and one which contained 256 aa (Fig. 1). The significance was estimated by simulation, permuting mutations among parental branches as previously described (Gayther et al. 1995; Thompson & Easton, 2002).

The robust method of calculating variance-covariance matrix was used in clustered-by-family analyses to control for observations that were not independent within families when assessing for the effect of exogenous factors (Lin & Wei, 1989). We also used a propensity score method to control for potential biases due to missing questionnaires, which were assumed to be missing at random (Rosenbaum & Rubin, 1983). Analyses were performed using Cox proportional hazards regression fitted by using the inverse of this probability of having a missing questionnaire as a weighting factor. Data analysis was also performed by use of the STATA software (Stata Corp., 2001) and SAS software data management systems (SAS, version 8, Cary, NC).

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Table 1. Relative risks of breast cancer according to *ATM* (for AT-mutated gene) heterozygote status and mutation type

According to ATM heterozygote status

	O	E	RR	(95% CI)	H	Trd
All female relatives	28	18·6	1·50	(1·00–2·17)		
obligate-HetATM	9	2·27	3·96	(1·81–7·53)	0·01	0·02
50% HetATM	5	5·31	0·94	(0·30–2·20)		
25% HetATM	3	2·96	1·01	(0·20–2·96)		
Non-HetATM	11	8·07	1·36	(0·68–2·44)		
Female relatives <45 years						
All female	9	3·33	2·70	(1·23–5·13)		
obligate-HetATM	5	0·59	8·43	(2·73–19·8)	0·01	0·02
50% HetATM	0	0·84	—	—		
25% HetATM	2	0·52	3·87	(0·43–13·9)		
Non-HetATM	2	1·38	1·45	(0·16–5·23)		
Female relatives ⩾45 years						
All female	19	15·3	1·24	(0·75–1·94)		
obligate-HetATM	4	1·68	2·39	(0·64–6·10)	0·36	0·32
50% HetATM	5	4·47	1·12	(0·36–2·61)		
25% HetATM	1	2·45	0·41	(0·01–2·27)		
Non-HetATM	9	6·69	1·34	(0·61–2·55)		

According to mutation type and ATM heterozygote status

	O	E	RR	(95% CI)	RR_w	(95% CI)
All type						
obligate-HetATM	9	2·27	3·96	(1·81–7·53)	2·43	(1·32–4·09)
50% HetATM+25% HetATM	8	8·37	0·96	(0·41–1·88)		
Truncating						
obligate-HetATM	5	1·36	3·68	(1·18–8·58)	1·93	(0·78–3·95)
50% HetATM+25% HetATM	4	5·86	0·68	(0·18–1·75)		
Missense or in-frame						
obligate-HetATM	1	0·27	3·70	(0·05–20·6)	1·96	(0·03–10·9)
50% HetATM+25% HetATM	0	0·50	—			

obligate-HetATM = relatives who are obligate heterozygotes for *ATM*
50% HetATM = relatives with a 0·5 probability of being heterozygotes for *ATM*
25% HetATM = relatives with a 0·25 probability of being heterozygotes for *ATM*
non-HetATM = relatives not carriers
O = observed number of cases
E = expected number of cases
RR = relative risk
RR_w = RR weighed on the *a priori* probability of being heterozygotes for *ATM*
H = *P*-value of heterogeneity test
Trd = *P*-value of trend test

Results

Thirty-four of the 35 families contacted agreed to participate in this study. The 34 families included 1,423 relatives of AT patients (mean 42 per family, SD = 19 and a total of 64 492 person-years) with information available concerning demographic characteristics and the occurrence of any cancer. Eighteen of 29 breast malignancies reported in families were confirmed by pathological records and, in all of those there was complete agreement between the case-report and the pathological-record. DNA samples were collected from 401 individuals and this allowed us to classify 412 other individuals as either obligate-HetATM or non-HetATM. The mean ages of the groups of relatives for each HetATM status were similar (data not shown), and the overall mean age was 45·4 years.

According to ATM heterozygote status

BC was the most frequently reported cancer, with a total of 29 cases, 28 in females and one in males. The male subject with BC was obligate HetATM. There was an increased BC risk in obligate HetATM females of 3·96 (95% CI: 1·81–7·53, P=0·001) and a slightly increased BC risk (not significant) in the obligate non-HetATM females (1·36, 95% CI: 0·68–2·44) (table 1). No increased risk of BC was observed among the 25% and 50% HetATM groups.

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The RR of BC in obligate HetATM women younger than 45 years was 8·43 (95% CI: 2·73–19·8, $P<0·001$) and 5·85 (95% CI: 0·96–61·4) after adjustment on non-HetATM (data not shown). Females aged 45 or over had an increased risk of BC of 2·39 (95% CI: 0·64–6·10) (RRadj=1·77, data not shown).

According to type of mutation

The *ATM* mutation was assessed in 54 of the 69 (maternal and paternal) branches from the 34 AT families. No lymphoblastoid cell line was available from the AT child or from one or their parents for 15 branches. 45 mutations were detected of which 34 were distinct: 29 resulted in premature termination codons; two were in-frame deletions, in both proteins the PI-3 kinase domain remains intact encoded for by the in-frame mutated allele; and three were missense mutations, all in or around the region encoding the PI-3 kinase domain of the ATM protein (Cavaciuti et al. 2005).

The frequencies of truncating mutation, missense mutation or an in-frame deletion are respectively 86·7% (39/45) and 13·3% (6/45). The RR of BC associated with being an obligate-HetATM was similar for both types of mutation: 3·68 for individuals carrying truncating mutations; 3·70 for those carrying missense or in-frame mutations. For the group with uncertain *ATM* heterozygosity (i.e. both the 50% and 25% HetATM groups combined), the RR of BC was not increased. The RR of BC was also estimated based on the presence of a truncating mutation in the different sections of the *ATM* gene (Fig. 1). BC risk was significantly associated with the location of the truncating mutation ($P=0·006$), i.e. the truncating mutations in individuals with BC did not appeared randomly scattered throughout the *ATM* gene. The RR_w of BC was particularly high for mutations in 4 sections of the ATM protein, three highest values correspond to domains of the ATM protein that have been previously characterized: the p53/BRCA1 binding domain, the β-adaptin binding domain and the end of the FAT binding domain (Stankovic et al. 2002). We were unable to identify any significant trend or difference in the RR estimates between these four sections. However it should be noted that the power of this study for detecting differences between sections was very low because of the small sample sizes.

According to exogenous factors

The reproductive variables studied were age at menarche, age at first childbirth, number of children, number of abortions (spontaneous and induced) and age at menopause. To evaluate the effect of past exposure to radiation, women who had received preventive or diagnostic chest X-rays (e.g. tuberculosis screening, broken ribs etc.) five or more years before the diagnosis of cancer or before the interview were considered to have been exposed to radiation.

We investigated the main effects of reproductive life factors on all women. As expected, due to the small number of BC cases none of the relative hazard (RH) estimates were significantly different from one. RHs associated with reproductive factors like age at menarche, age at 1st childbirth, number of children and menopause for BC were in the usual direction, that is greater with an early age at menarche, a late age at first childbirth, nulliparity and premenopausal status. A decreased point estimate of BC risk was associated with the use of oral contraceptives (RH=0·3; 95% CI: 0·1–1·7). Very few women with BC (20%) had been exposed to radiation compared with controls (72·5%), thus exposure to radiation significantly decreases the risk of BC (RH=0·1; 95% CI: 0·02–0·4). This estimate did not change according to the age at first exposure. A similar point estimate was found when women who had received radiation in the form of a mammography were considered (RH=0·2; 95% CI: 0·02–1·6).

The only test for interaction of ATM heterozygote status with exogenous factors that was statistically significant was age at 1st childbirth ($P=0·03$). Late age at first childbirth was only associated with a significantly high RH among the obligate HetATM (RH=12·9; 95% CI: 1·3–126). The point estimates of the hazard ratios associated with body mass index (BMI) differed according to ATM heterozygote status. Indeed, the point estimate associated with a BMI >24 kg/m^2 compared to a BMI $\leqslant 24$ kg/m^2 was 0·7 for the non-HetATM and 2·2 for the obligate HetATM. The point estimate of BC risk associated with age at menarche >15 years was lower for the obligate HetATM (RH=0·4) than for the non-HetATM (RH=0·8). Due to the small number of non-HetATM with BC, we could not assess the variation of BC associated with use of the contraceptive pill, exposure to ionizing radiation according to ATM heterozygote status.

Discussion

In agreement with the literature (Swift et al. 1987, 1991; Pippard et al. 1988; Børresen et al. 1990; Morrell et al. 1990; Athma et al. 1996; Stankovic et al. 1998), our studies based on AT families living in France also found that the risk of BC was 3·6-fold higher in HetATM women. The BC risk did not differ significantly according to the type of *ATM* mutation carried by the AT family members but appeared associated with the position of some truncating mutations in certain binding domains of the ATM protein (i.e. p53/BRCA1, β-adaptin and FAT binding domains). We also investigated the effect of exogenous factors, such as reproductive life factors and exposure to ionizing radiation, on the risk of BC according to ATM heterozygote status. As expected, our results did not give evidence for interaction (except for age at 1st full-term pregnancy), but risk assessments according to ATM heterozygote status can only be considered as exploratory due to the small numbers of individuals in the study.

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The calculations of expected numbers of cancer are known to be sensitive to the reference population used. Because national incidence data are not available in France, estimated incidences between 1978 and 1992 were used as the reference population. This might induce an over-estimate of the expected number of cancer among at-risk individuals before 1978 (mostly grandparents, grandaunts/uncles and great grandparents of AT children) and an under-estimate of this number among exposed individuals after 1992 (mostly parents and aunts/uncles) since the incidence rate has been increasing in West European countries for a number of decades for most of cancer (Parkin et al. 1993). This might bias the RR estimates but did not affect the comparisons between subgroups.

A poor sensitivity of self-reported family history of cancer (i.e. under-reporting) may have led to an under-estimate of the relative risk of cancer. However, most of the BC cases were verified and BC has been reported with great accuracy in numerous other studies (e.g. Theis et al. 1994). We were unable to verify the disease status of relatives declared unaffected as France has no national cancer registry. However, it has been estimated that about 98% of negative family history were correct (Aitken et al. 1995; Ziogas & Anton-Culver, 2003).

The point estimate of BC risk appeared to be higher in female relatives younger than 45 years old than in those aged 45 years or over. This was the contrary to the findings of Athma et al. (1996) and FitzGerald et al. (1997) where there was no evidence for an increased frequency of HetATM in women with early onset of BC. However, it agreed with others (e.g. Broeks et al. 2000; Olsen et al. 2001) where younger women were estimated to have a higher risk of developing a BC than older (~9-fold increased risk in women less than 45 years in Broeks et al. (2000) and 7-fold increased risk in those less than 55 years in Olsen et al. (2001)).

Even though the power of our study for detecting differences between subgroups was limited, the RR point estimates give no indication of there being different risks for BC associated with either truncating or missense and in-frame mutations. However, as there were few missense and in-frame mutations considered in this study, our estimate was imprecise. Our finding on the association of the BC risk with the position of some truncating mutations in certain binding domains of the ATM protein was difficult to interpret. One possible explanation was that *ATM* mRNAs carrying mutations in such domains are preferentially eliminated resulting in haplo-insufficiency and therefore increased cancer risk. An alternative possibility was that this increased risk may be associated with the absence of certain binding domains or the presence of altered binding domains in a truncated form of the ATM protein which is produced in cells carrying such mutations. The mechanism by which the production of a truncated protein affects the ability of the normal ATM protein to function is unknown. The analysis of the transcription and translation of such *ATM* variants will be necessary to understand the underlying molecular mechanisms.

Our results on the main effects of reproductive life factors on the risk of BC among AT child relatives were consistent with those of previous studies on BC in the general population (Kelsey & Horn-Ross, 1993) for the age at menarche, age at first childbirth, nulliparity and menopausal status. Our findings that the risk of BC decreased with use of the contraceptive pill seemed to contradict previous studies on BC in the general population (Anonymous, 1996). When the BC risk according to ATM heterozygote status was considered, age at 1st childbirth seemed to have a stronger effect on obligate HetATM than on non-HetATM. However, the numbers were very small and the interaction detected between age at 1st childbirth and ATM heterozygote status might be due to chance.

The increased risk associated with a high BMI among the HetATM may be explained by the role of estrogens. Indeed, overweight women have been shown to have a higher level of circulating estrogens than thin women, which may have a more pejorative effect on genetically susceptible breast cells. The number of children appeared to have a similar effect on HetATM and on non-HetATM. Some studies observed a similar effect of parity among women with and without a family history of BC, others found that multiparity was not more protective than nulliparity among women with a family history of BC (e.g. Andrieu & Demenais, 1997; Chang-Claude et al. 1997; Andrieu et al. 2000; Narod et al. 1995). Some studies on women carrying the hereditary BC gene mutations, BRCA1 or BRCA2, found that the risk of early BC increased with each successive birth (e.g. Jernstrom et al. 1999). The potential effect of parity on genetically susceptible breast cells remains unclear and needs further investigations.

Our finding on the risk of BC being lower in HetATM who had received radiation to chest or breasts when compared with HetATM who had not received radiation was not in agreement with results of Swift et al. (1987, 1991). However, only 15 cases among 28 BC cases in women in our study could be interviewed. Thus, the low hazard ratios associated with radiation might be explained by differential survival according to susceptibility to radiation among BC cases. Indeed, if those susceptible to radiation would develop a more fatal BC than would those non-susceptible, one may have expected to observe a lower number of medical exams involving ionizing radiation among surviving BC. However, to our knowledge, there is no published study on a potential difference in survival between radio-induced and non radio-induced BC.

As a general conclusion, the increased risk of BC in HetATM women does not appear to justify a separate screening program to that already available to women with a first-degree relative affected by BC, as their risks have similar amplitude. Chest X-rays did not appear to be a risk factor for BC in our study. However, it is important to note that as our study was limited by sample size, more

powerful studies, using retrospective or prospective data sets pooled from international sources will be needed to confirm these observations and in particular examine whether the risk depends on the type and position of the ATM mutation and the impact of exogenous factors.

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